

BENZOTRIAZOLE MEDIATED TRANSFORMATIONS
OF ANILINES, PHENOLS, AND RELATED COMPOUNDS

BY

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1991

To my wife, Huixia, with love

ACKNOWLEDGEMENTS

I am deeply indebted to my advisor, Professor Alan R. Katritzky, for his invaluable guidance, encouragement, and trust over the years. It has been a pleasure working with him.

I would also like to take this opportunity to express my sincere gratitude to Drs. William M. Jones, Eric J. Enholm, David E. Richardson, and Bruce R. Stevens for their helpful suggestions and the time they have spent as my supervisory committee members.

I would like to thank Drs. Jamshed N. Lam, John V. Greenhill, Stan Rachwal, Wei-Qiang Fan, and Phil Harris for their valuable corrections and suggestions during the preparation of the manuscript of this thesis. Special thanks are due to Jamshed for all his help during these years.

Thanks go to my "neighbor" (Dr. Subbu Perumal), the time we worked together is always memorable, and to "buddy system" member Wojtek for the evenings we spent in the lab. To the people in Leigh Hall during these years, Bogumila, Shibli, Sutha, Yannis, Hassan, Karoly, thanks for the discussions, companionship, and friendship.

I am indebted to my family for all the love, help, and encouragement, without which, I would not have had a

chance to get into college, let alone a chance to study in the United States.

Last but not least, I am deeply grateful to my wife, Huixia, for standing by me through these years, for understanding, for criticizing, and above all for everything she has done for me.

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Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

BENZOTRIAZOLE MEDIATED TRANSFORMATIONS OF ANILINES,
PHENOLS, AND RELATED COMPOUNDS

BY

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May 1991

Chairman: Alan R. Katritzky, FRS
Major Department: Chemistry

The use of benzotriazole as a synthetic auxiliary has been extended to conjugated systems. A benzotriazol-1-ylmethyl group was incorporated into anilines, phenols, and phenol ethers. The parent benzotriazole derivatives have been elaborated via lithiation. The displacement of the benzotriazole group in these parent derivatives and in the lithiated derivatives by various nucleophiles has been investigated.

N-(Benzotriazol-1-ylmethyl)arylamines were converted into bis(4-aminoaryl)methanes. Anilines reacted with 1-hydroxymethylbenzotriazole to give 4-(benzotriazol-1-ylmethyl)anilines and methylenebisanilines. The benzotriazolyl moiety in 4-(benzotriazol-1-ylmethyl)-

anilines was displaced successfully by anilines, 1,3-dimethoxybenzene, 1,3,5-trimethoxybenzene, pyrroles, and indoles to give diarylmethanes.

The methylene groups in 4-(benzotriazol-1-ylmethyl)anilines were deprotonated via lithiation and the anions were trapped with various electrophiles. The benzotriazole group in the lithiated derivatives was displaced by anilines and indole to afford leuco dyestuffs.

A (α -benzotriazolyl)alkyl group was incorporated into the phenol systems either by the direct reaction of phenols with 1-hydroxymethylbenzotriazole or by the condensation of naphthols, aldehydes, and benzotriazole to give the ortho substituted derivatives. The protection of the phenolic hydroxyl group with trimethylsilyl chloride enabled an efficient substitution at the acidic methylene groups via lithiation in o-(benzotriazol-1-ylmethyl)-phenols. The displacement of the benzotriazole group in the parent and in the lithiated derivatives by Grignard reagents and by hydride ion from lithium aluminum hydride allowed an efficient synthesis of substituted phenols.

Phenol ethers were similarly benzotriazol-1-yl-methylated, giving p-(benzotriazol-1-ylmethyl)phenyl methyl ethers. The methylene groups were easily substituted with electrophiles via lithiation. The benzotriazole group was displaced by Grignard reagents and

by nucleophilic aromatic compounds such as anilines and indole.

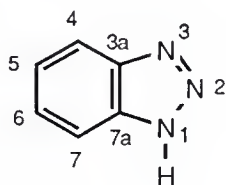
The triazole ring of benzotriazole in the α -benzotriazol-1-yl carbanions underwent smooth opening, followed by the loss of a molecule of nitrogen, to give an anion, which was trapped by electrophiles inter- or intramolecularly to afford imines or heterocycles.

CHAPTER I GENERAL INTRODUCTION

1.1 Benzotriazole as a Synthetic Auxiliary

Benzotriazole (1.1) has attracted considerable attention because of its theoretical interest, and synthetic values, as well as for its numerous applications in industry and agriculture. Benzotriazole can be viewed as the benzo derivative of 1H-1,2,3-triazole in which the triazole moiety has its two carbon atoms shared with the benzene ring. One important feature of benzotriazole is the strong electron-withdrawing nature of the nitrogen-nitrogen double bond. This feature is reflected in the high acidity of benzotriazole (pK_a 8.35) [88JA4105], which is comparable to that of uracil (pK_a 9.45) [56JA5292] or phenol (pK_a 9.97) [59MI1], rather than to those of similar heterocyclic systems containing fused five-membered rings such as pyrrole (pK_a 23) [81JOC632], carbazole (pK_a 19.9) [81JOC632], or benzimidazole (pK_a 13.2) [58JCS1974]. This acidity gives benzotriazole two very important characteristics. One is that it shows higher reactivity towards many types of reactions such as nucleophilic substitution and nucleophilic addition reactions. Another

important characteristic is that the benzotriazole anion has been shown to be a good leaving group.



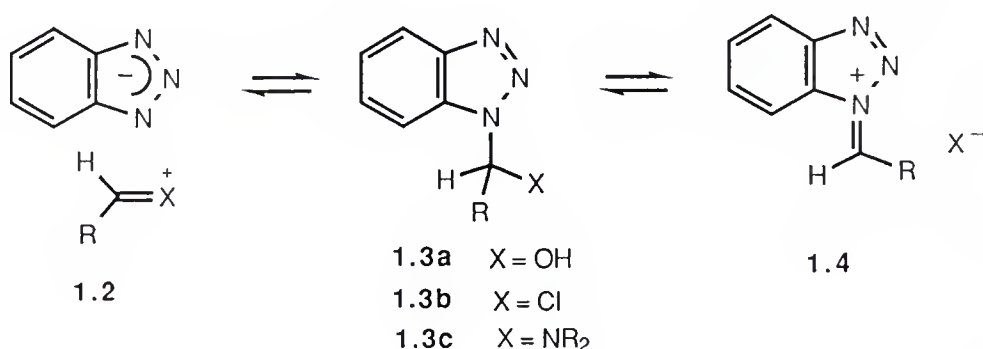
1.1

Figure 1.1 Benzotriazole

Benzotriazole readily adds to aliphatic aldehydes to give 1-(α -hydroxyalkyl)benzotriazoles (1.3a) [87JCS(P1)791]. Conversion of the hydroxy derivatives to the corresponding chloro derivatives 1.3b was achieved with thionyl chloride [52JA3868, 87JCS(P1)811]. Benzotriazole has also been shown to condense directly with dialkylamines [46JA2496, 75JCS(P1)1181] or with arylamines [52JA3868, 55JA5386, 76IJC(B)718, 80MI1] and formaldehyde or other aldehydes [87JCS(P1)805, 89JCS(P1)225] to give Mannich-type adducts (1.3c).

Scheme 1.1 illustrates the alternate ways in which the benzotriazole adducts can ionize. When X is an electron-donor group, in particular a nitrogen-linked substituent as 1.3c, ionization occurs to form the benzotriazole anion. When X is itself a leaving group, for example, a halogen, then the benzotriazole nitrogen atom

can assist the ionization of X as an anion, leaving the benzotriazole as part of the cationic species. The chlorine atom in 1-chloromethylbenzotriazole (1.3b; R = H), for example, has been easily displaced by carbon, nitrogen, oxygen, phosphorus, and sulfur nucleophiles [87JCS(P1)781]. It has been amply demonstrated that ionizations of both types occur with many benzotriazole derivatives.

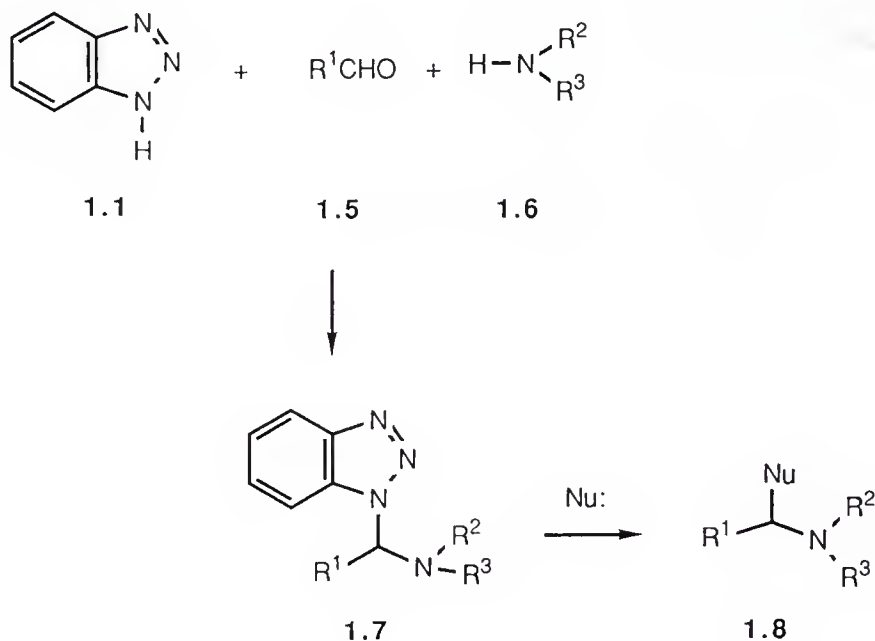


Scheme 1.1

The use of benzotriazole as a synthetic auxiliary is based upon the above rationale that the reactive benzotriazole can be used as an anchor and as an activator of neighboring bonds to construct a molecular assembly. The benzotriazole moiety could then be easily displaced by cleavage of the C-N bond to afford useful compounds.

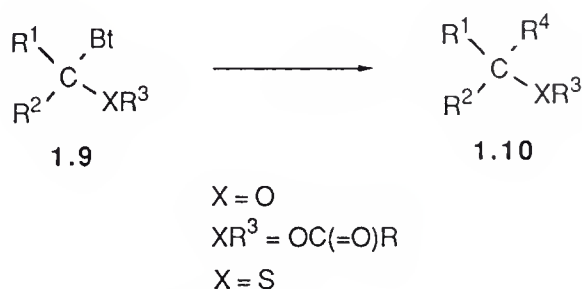
In our laboratory, the use of benzotriazole as a synthetic auxiliary has been explored to a large extent. It is used for the elaboration of various nitrogen-

containing compounds. The Mannich-type condensation of benzotriazole, an aldehyde, and an NH- compound afforded adducts of type 1.7. The subsequent displacement of the benzotriazole moiety in the adduct 1.7 by a nucleophile has enabled the preparation of amines [87JCS(P1)799, 87JCS(P1)805, 89JCS(P1)225, 89S31], hydrazines [89JCS(P1)2297], N,N-disubstituted hydroxylamines [89JCS(P1)225], N-substituted amides [88JCS(P1)2339, 88JOC5854] or thioamides [88JOC5854, 88TL1755], and amino acid derivatives [89CC337, 89S323] (Scheme 1.2).



Scheme 1.2

The utility of benzotriazole as a synthetic auxiliary has been extended to the preparation of oxygen compounds such as ethers and esters [89JOC6022, 90JCS(P1)1717], as well as to the preparation of thiol ethers [91UP1].

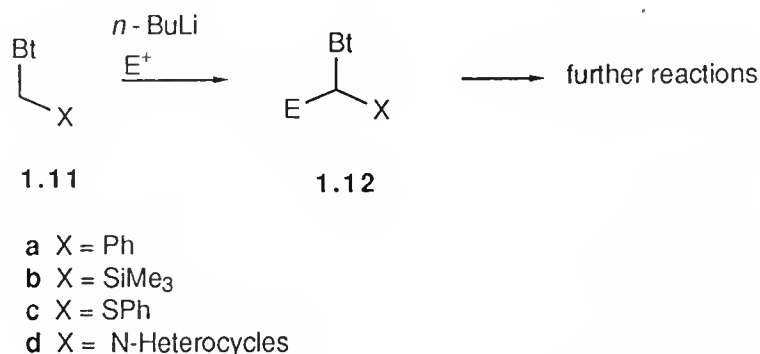


Bt = benzotriazol-1-yl

Scheme 1.3

Another aspect concerning the use of benzotriazole as a synthetic auxiliary is the elaboration of the benzotriazole adducts before the displacement is enforced. Heteroatom facilitated lithiation has become an increasingly important tool in synthetic chemistry [69CRV693, 70MI1, 73MI1, 74MI1, 74MI2]. The strong electron withdrawing ability of the benzotriazole ring makes the α -groups in certain systems acidic and thus capable of undergoing deprotonation to generate a carbanion, which can then be trapped with a variety of electrophiles. The subsequent removal of the benzotriazole

group leads to functionalized molecules. Thus, it was shown that the benzotriazole adducts of type 1.11 with (a) $X = \text{Ph}$ [90MI1], (b) $X = \text{SiMe}_3$ [90MI1], (c) $X = \text{SPh}$ [87JCS(P1)781], and (d) $X = \text{an N-linked heterocycle}$ (pyrrole, indole, and carbazole) [89JHC829] undergo smooth lithiation at the methylene groups to give derivatives of type 1.12 when trapped with various electrophiles.

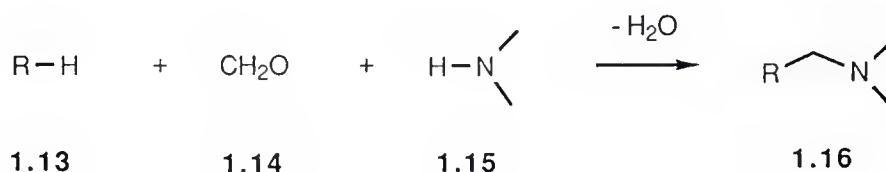


Scheme 1.4

1.2 Overview on the Extended Mannich Reactions: α -Amidoalkylations

The Mannich reaction has been an important tool for the synthesis of new compounds and has been well reviewed in the literature [42OR303, 56AG265, 59MI2, 60MI1, 73S703, 90T1791]. In its most general representation, formaldehyde (rarely other aldehydes) is condensed with a primary or secondary amine and a compound (substrate) containing an active hydrogen atom (usually a CH, sometimes an NH)

(Scheme 1.5). The significance of the Mannich reaction is that the Mannich bases are easily obtained and are sometimes employed as such. On the other hand, the Mannich bases are also very reactive and are used as synthetic intermediates to numerous other compounds such as amines, amino-alcohols, and heterocycles. The most intensively investigated substrates involve alkyl ketones, phenols, carboxylic acid derivatives, and NH-heterocyclic compounds.

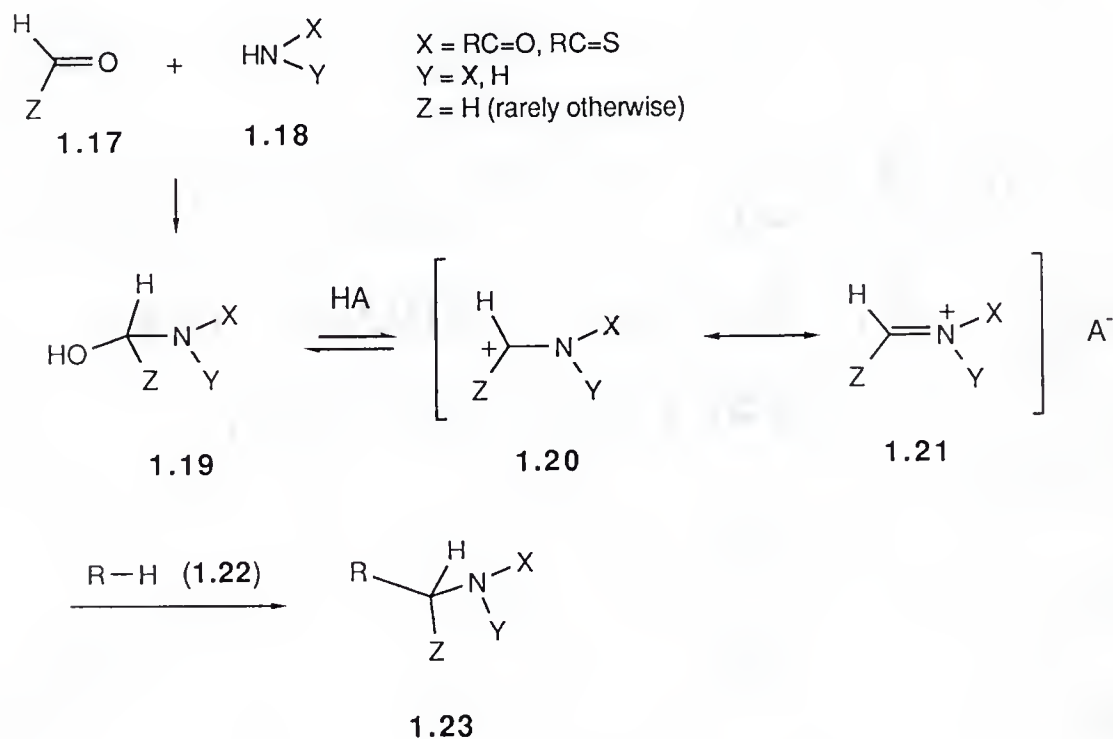


Scheme 1.5

Important extensions of the Mannich reaction where amides, imides, ureas, thioureas, etc. replace the amine component, known as α -amidoalkylations, are also well documented in the literature [63MI1, 64AG909, 65OR52, 70S49, 73S243, 84S85]. Acetanilide, phenols, and phenol ethers as well as other substrates have been employed as the active CH- compounds in these Mannich condensations with aldehydes and amides or imides under various conditions. For acetanilide and phenol ethers, the amido-alkylation occurs at the para-position or at both the

ortho- and the para-positions depending the reaction conditions and the reagents used [66JOC133, 69CC376]. For phenols, the ortho-substituted derivatives are obtained unless both ortho positions are occupied, in which case the Mannich reaction occurs at the para-position [57RTC249].

The α -amidoalkylation reaction is invariably acid-catalyzed. The first step consists of the addition of the NH group to the carbonyl carbon of formaldehyde (or rarely another aldehyde) giving rise to an α -alkylol compound 1.19. This derivative is converted (via acid catalysis) into a carbonium/imonium ion (1.20 $\leftrightarrow$ 1.21) which then reacts with the substrate to yield the condensation product 1.23.



Scheme 1.6

Compounds 1.19 can be isolated prior to use. These and other analogous reagents include N-hydroxyalkylamides [69JOC14], N-alkoxyalkylamides [66JOC133], N-haloalkylamides [63JOC2925], and N,N'-(arylmethylene)bisamides [57RTC249]. In most of these cases, the carbonyl compound has been formaldehyde.

1.3 General Outlook

The aim of the overall project is briefly mentioned in this section. The specific details are discussed more thoroughly in the respective chapters.

Work in our laboratory concerning the use of benzotriazole as a synthetic auxiliary has succeeded in the elaboration of many types of nitrogen containing compounds as well as oxygen and sulfur containing compounds. In all these cases, the benzotriazole ring and a heteroatom bearing an electron pair are connected to the same carbon. The lone electron pair assists in the displacement of the benzotriazole anion; a subsequent attack by a nucleophile affords the products. Until now, systems in which the benzotriazole ring and a heteroatom are connected through a conjugated system have remained virtually unexplored.

The objective of the present project is to investigate the use of benzotriazole as a synthetic auxiliary in a conjugated system. A benzene ring is

suitable for such a conjugated system. Amino, hydroxy, or alkoxy groups should activate the benzene ring for the construction of the benzotriazole adducts and assist in the subsequent displacement of the benzotriazole group by nucleophiles.

CHAPTER II
BENZOTRIAZOLE MEDIATED SYNTHESIS OF
METHYLENEBISANILINES

2.1 Introduction

2.1.1 Utilization and Synthesis of Methylenebisanilines and an Evaluation of Previous Methods

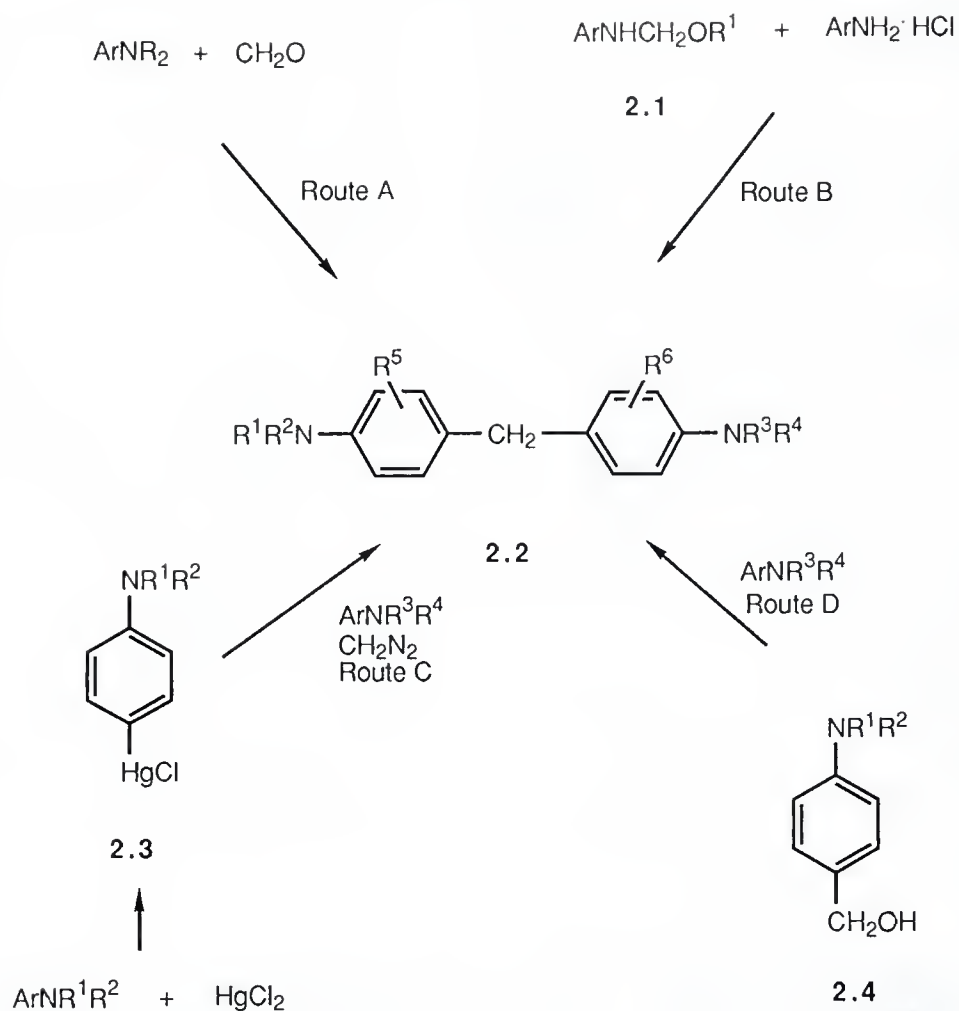
4,4'-Methylenebisanilines (2.2) represent a class of well known compounds. A large number of papers and patents exist which deal with the preparation and wide application of such compounds in polymers.

4,4'-Methylenebisaniline (2.2; $R^1-R^6 = H$) is used as a curing agent for epoxy resins and urethane elastomers [75JAP7439671, 88JAP6345242], as an intermediate in the preparation of polyurethanes [74JAP7428022, 87MI1], in the synthesis of polyamides [67FRP1474509, 88MI1], and also in the preparation of azo dyes [75MI1, 75USP3890257, 87MI2]. The dialkylaniline analogues (2.2; $R^1, R^2, R^3, R^4 \neq H$) have found applications in the production of dyes [79GEP2739953, 87ZOR1516] and recording materials [75GEP2446892, 84JAP59208546, 87MI3], as antioxidants for lubricating oils [77GEP2538445, 84JAP59230094], as curing agents for epoxy resins [66NEP6608593, 73JAP7344382,

85GEP3327712], and as electrically insulating composite materials [75BRP1396371, 85GEP3327711].

The symmetrical analogues of type 2.2 have been synthesized by several methods. The major methods include the reaction of an arylamine (or N,N-dialkyylaniline) with formaldehyde in the presence of concentrated hydrochloric acid (Route A) [14CB1161, 34JA1944, 35JA887, 54JOC1862, 55JCS83, 67JOC3101, 87JCR(S)194, 87MI4]; the reaction of an N,O-aminal 2.1 with an arylamine hydrochloride under acidic conditions (Route B) [88JCS(P1)1631]; the use of mercury reagents 2.3 (Route C) [79CC339, 80JCS(P1)1420]; and the use of 4-hydroxymethyl-N,N-dialkyylaniline (2.4) (Route D) [55MI1, 55MI2, 55MI3] (Scheme 2.1). Other methods include the reduction of appropriate 4,4'-diaminobenzophenones [50JA3586, 54MI1, 81JOC2579] or the corresponding thiones [74JOM359, 75JOC2694, 83JOC250, 85JA6121] and the alkylation of bisanilines [80MI2].

The syntheses and applications of unsymmetrical analogues are less common. There are only a few preparative methods for the unsymmetrical methylene-bisanilines. Compounds 2.3 [79CC339] and 4-hydroxymethyl-N,N-dialkyylanilines (2.4) [55MI1, 55MI2, 55MI3] react with a variety of arylamines to afford the unsymmetrical methylenebisanilines. Other methods involve an arylamine exchange [1894CB1804, 1900CB2586] or an alkylation of 4,4'-methylenebisaniline [82MI1].



Scheme 2.1

Most of the methods described above have some setbacks such as low yields, tedious work-up and purifications, or other synthetic limitations. The reaction between arylamines and formaldehyde (Route A) and

the reaction of N,O-aminals [88JCS(P1)1631] (Route B) give only symmetrical analogues. The reduction reactions are limited by availability of the starting materials. On the other hand, the alkylation of 4,4'-methylenebisaniiline often leads to a mixture which is difficult to separate and purify. The use of compound 2.3 affords good yields in some cases [79CC339], yet the specific reaction conditions prevent this method from wide-range application.

4-Hydroxymethyl-N,N-dialkylanilines (2.4) seem to be good reagents. However, they are extremely sensitive to traces of acids, especially at higher temperatures where they can decompose to the N,N-dialkylanilines and formaldehyde. Moreover, they are oxidized rather readily on exposure to air. Thus, they are not easy to handle and often give mixtures and very low yields of the desired products in the preparation of methylenebisaniilines [34JCS730].

2.1.2 Aim of the Work

Although the Mannich reaction has been an important tool in synthetic organic chemistry for many years, its application is subject to several limitations [42OR303, 60MI1, 73S703, 90T1791]. One such limitation is that the products initially formed in the condensation of formaldehyde with ammonia, or with a primary amine, undergo further transformations with participation of the

remaining N-H bonds leading to mixtures [57MI1, 60MI1, 65MI1]. To overcome these difficulties, several papers have recently reported efficient synthetic equivalents for methyleneimines (2.5). Thus it has been demonstrated that derivatives 2.6 with Y = alkoxy (2.6a) [83CC1109], Y = SAr (2.6b) [71JHC597, 80S1025, 81JCS(P1)1569, 84CC427], Y = CN (2.6c) [84TL1635, 85CC951, 85JA1698, 86TL1147], and Y = SiHR₂ (2.6d) [73TL2475, 84CC794, 84CC883, 84CC1055] can all eliminate the Y group to afford, in situ, reactive methyleneimines such as 2.5 or their protonated forms 2.7.

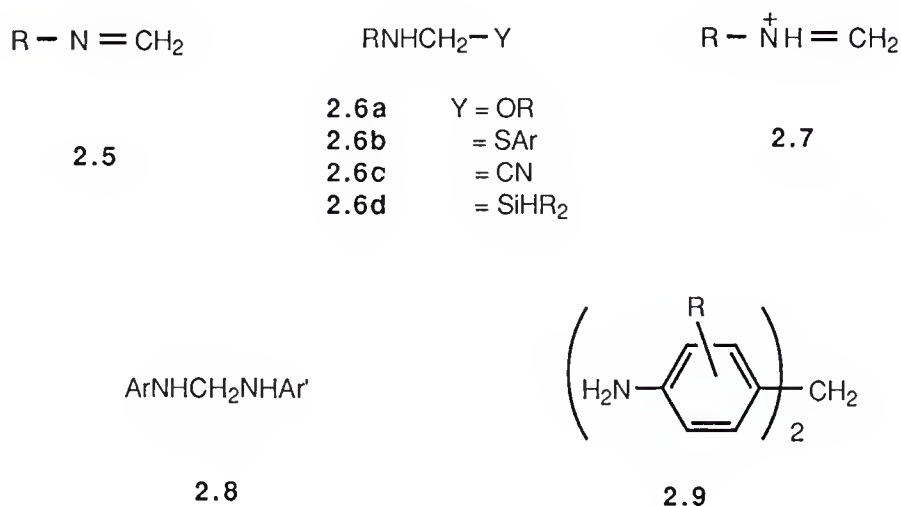


Figure 2.1 Synthetic Equivalents for Methyleneimines

Barluenga and co-workers have achieved monoalkylation of primary aromatic amines [83CC1109] and have synthesized

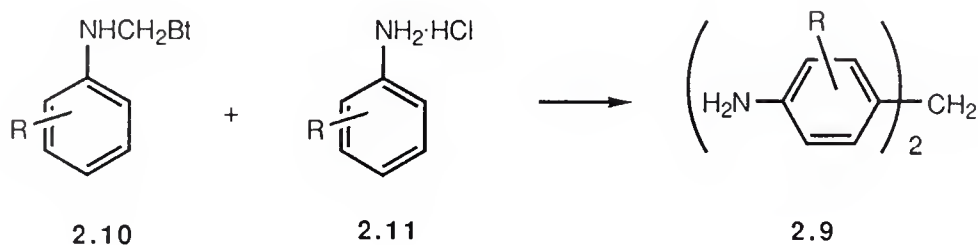
symmetrical and unsymmetrical bis(arylamino)methanes (2.8) [88CB1813] using the masked form 2.6a of a reactive methyleneimine. They have also reported a high yielding synthesis of N-(2-alkynyl)arylamines in a one-pot reaction of N-(methoxymethyl)arylamines with 1-alkynyllithium [89S33].

A comparison of the properties of benzotriazole with those of an alkoxyl group reveals similar roles played in certain types of reactions by these groups. The use of benzotriazole as a synthetic auxiliary has successfully achieved the alkylation of aromatic amines [87JCS(P1)799, 87JCS(P1)805, 90CJC446, 90CJC456], synthesis of aliphatic amines [89JCS(P1)225, 89S66, 90CB1443], the alkylation of hydroxyamines, hydrazines and amides [88JCS(P1)2339, 88JOC5854, 88TL1755, 89JCS(P1)225, 89JCS(P1)2297], and synthesis of tertiary propargylamines by reaction of N-(benzotriazol-1-yl)arylamines with 1-alkynyllithium [89S31].

In a recent report [88JCS(P1)1631], the amins 2.1 were easily converted into bis(4-aminoaryl)methanes (2.9) upon treatment with arylamine hydrochlorides (Scheme 2.1; Route B). This promoted us to investigate the use of benzotriazole for such a purpose.

Thus, one of the objectives of the present work is to investigate the use of benzotriazole as an alkoxyl equivalent, and consequently its use for the conversion of

N-(benzotriazol-1-ylmethyl)anilines (2.10) to bis(4-amino-aryl)methanes (2.9) (Scheme 2.2).



Scheme 2.2

Previous studies on the use of benzotriazole as a synthetic auxiliary have been for derivatives of type 2.12 in which the benzotriazole group and the heteroatoms are connected to the same carbon. In these derivatives, the lone electron pair from the heteroatom is believed to assist the displacement of the benzotriazole group to give stabilized cations 2.13. The systems in which the benzotriazole group and the heteroatom are connected through a conjugated system of type 2.14 have remained virtually unexplored.

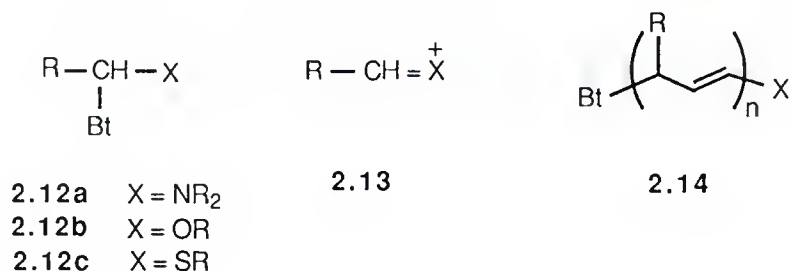
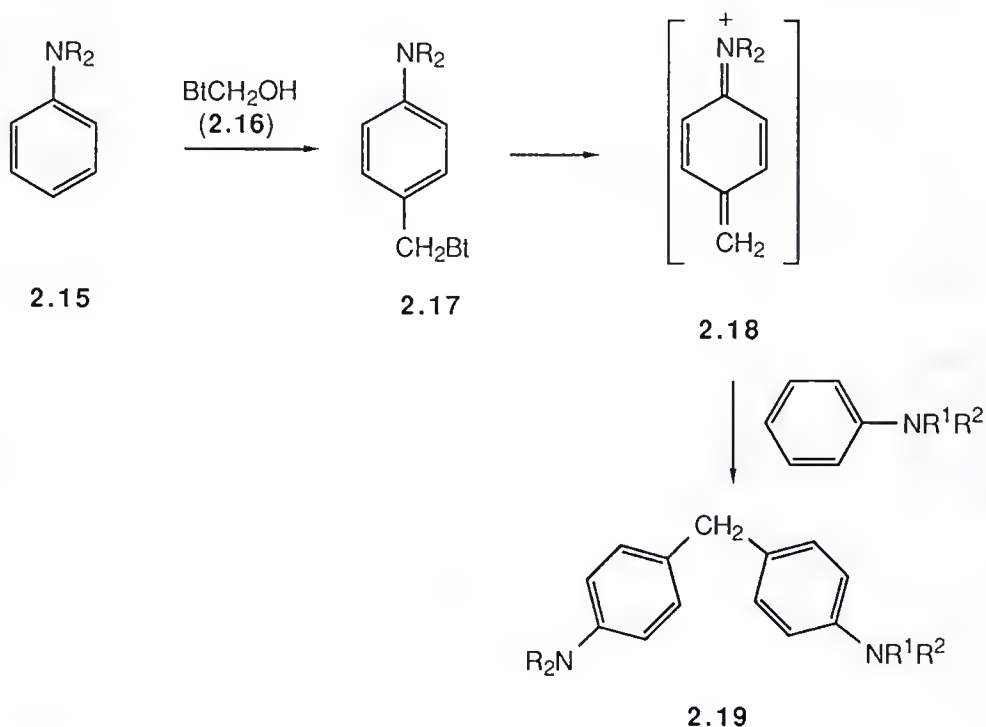


Figure 2.2 Benzotriazole Derivatives

Therefore, another aim of this work is to investigate the use of benzotriazole as a synthetic auxiliary in a conjugated system. In particular, anilines were chosen as the substrates in which the phenyl ring was the conjugated backbone and the amino group was the assisting group. An amino or a dialkylamino group should activate the benzene ring in the electrophilic substitution reactions. The direct alkylation of anilines by a benzotriazol-1-ylmethyl group would be possible. The lone electron pair from the amino nitrogen would then assist the leaving of the benzotriazole group. A subsequent attack by an aniline would lead to a variety of 4,4'-methylenebisanilines (Scheme 2.3).

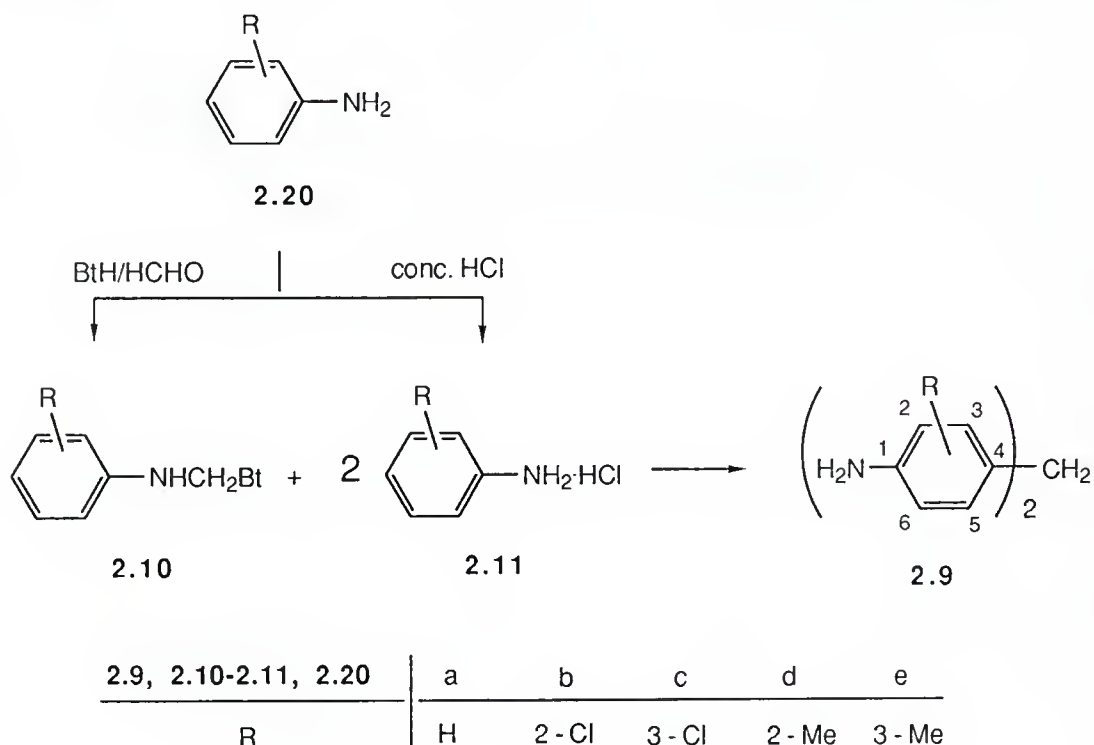


Scheme 2.3

2.2 Results and Discussion

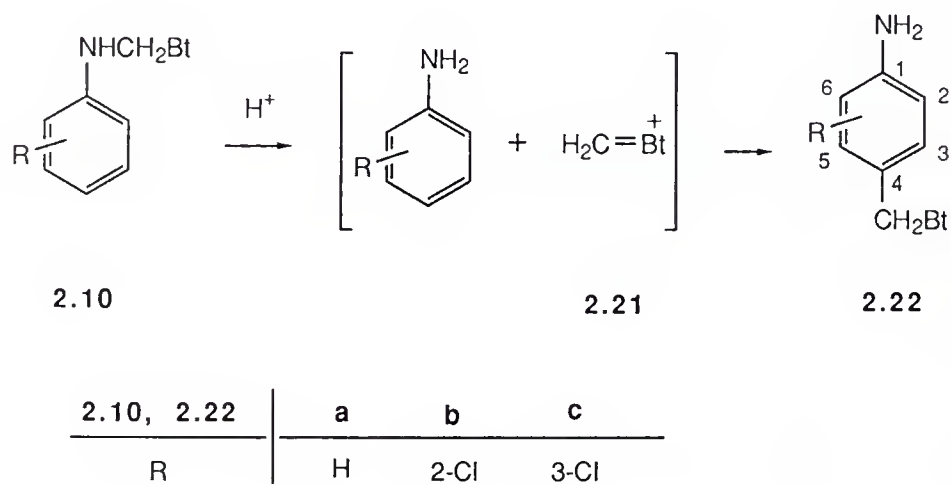
2.2.1 Preparation of Bis(4-aminoaryl)methanes (2.9) using N-(Benzotriazol-1-ylmethyl)arylamines

Bis(4-aminoaryl)methanes (2.9) were obtained from reaction of N-(benzotriazol-1-ylmethyl)arylamines (2.10) and two equivalents of arylamine hydrochlorides (2.11) in a 50% aqueous methanol solution (Scheme 2.4). The adducts 2.10 were readily prepared by stirring a mixture of the arylamine, formaldehyde and benzotriazole in methanol at room temperature [87JCS(P1)799]. The arylamine hydrochlorides 2.11 were obtained by mixing the corresponding arylamines with concentrated hydrochloric acid.



Scheme 2.4

However, in two cases, 4-(benzotriazol-1-ylmethyl)-2-chloroaniline (2.22b) and 4-(benzotriazol-1-ylmethyl)-3-chloroaniline (2.22c) were obtained as by-products in yields of 26% and 7%, respectively. Heating N-(benzotriazol-1-ylmethyl)aniline (2.10a) alone in 50% aqueous methanol in the presence of one equivalent of concentrated hydrochloric acid, followed by basic hydrolysis, afforded 4-(benzotriazol-1-ylmethyl)aniline (2.22a) in a yield of 59%. Compounds 2.22 could be intermediates in the preparation of bis(4-aminoaryl)methanes (2.9) and may be formed from the reactive cation 2.21. Supporting evidence for this was the formation of compound 2.9a from the reaction of 2.22a with 2.11a. Other mechanisms are also possible such that proposed by Wagner [54JOC1862] for the acid-induced reactions of formaldehyde and amines.



Scheme 2.5

Table 2.1 Preparation of Bis(4-aminoaryl)methanes (2.9)

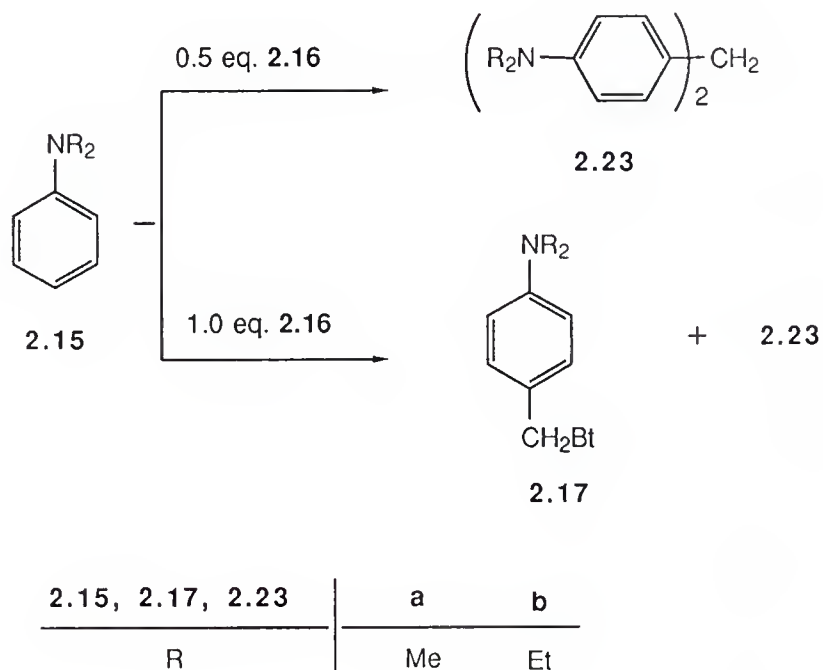
Product	Yield ^a (%)	M.p. (°C)	Lit. m.p. (°C)
2.9a	58	90-92	91.5-92 [35JA887]
2.9b	44	107-109	110 [14CB1161]
2.9c	32	99-101	100-103 [55JCS83]
2.9d	50	155-157	149-155 [35JA887]
2.9e	50	117-119	119-120 [34JA1944]

^a Isolated yields.

2.2.2 Preparation of 4-(Benzotriazol-1-ylmethyl)anilines

N,N-Dimethylaniline and 1-hydroxymethylbenzotriazole (2.16) when heated under reflux in acetic acid for 5 min (following the conditions reported for the tritylation of aniline hydrochloride with triphenylmethanol [63OSC47]) afforded a mixture of 4-(benzotriazol-1-ylmethyl)-N,N-dimethylaniline (2.17a) and 4,4'-methylenebis-(N,N-dimethylaniline) (2.23a) (Scheme 2.6). Evidently, 2.17a undergoes displacement of the benzotriazole group by a second molecule of N,N-dimethylaniline under the acidic conditions. The lone electron pair of the amino nitrogen atom in 2.17 assists in the displacement of benzotriazole to form the reactive intermediate 2.18 (Scheme 2.3), which

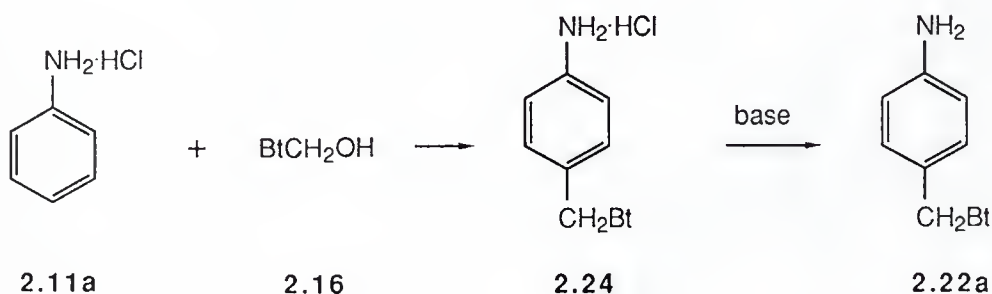
then reacts with N,N-dialkylaniline to give the bis-product. When two equivalents of N,N-dialkylaniline were reacted with 2.16, only the bis-product 2.23 was isolated.



Scheme 2.6

If the electrons on the nitrogen are less available, the benzotriazole adducts can be isolated in higher yields. Thus, aniline hydrochloride was heated under reflux in acetic acid with 2.16 to give only the alkylated product 2.22a (Scheme 2.7). Obviously the coordination of

the electron pair on the nitrogen to the proton in compound 2.24 prevents the displacement of the benzotriazole group. When N,N-dimethylaniline was treated with one equivalent of concentrated hydrochloric acid, then refluxed with one equivalent of 2.16 in 1-propanol, the yield of 2.17a was increased dramatically, although a small percent of bis-product 2.23a was still formed.



Scheme 2.7

The mixtures of the benzotriazole adducts 2.17 and the bis-products 2.23 were easily separated due to their different solubilities in hot hexane; the bis-products 2.23 dissolved, but the benzotriazole adducts 2.17 were insoluble and could easily be isolated by filtration.

The structures of the benzotriazole adducts 2.17 and 2.22 were confirmed by their spectral and analytical properties. The ^{13}C NMR spectra showed the characteristic

patterns for 1-substituted benzotriazole derivatives. The quaternary carbons, C-3a and C-7a, of the benzotriazole moiety appeared between 143.1-146.3 ppm and between 132.4-132.8 ppm, respectively. The regio chemistry of these adducts was determined from the number of resonances in the ^{13}C NMR spectra. The most indicative methylene groups, attached to an electron-withdrawing benzotriazole group, appear in the ^{13}C NMR spectra between 48.0-52.1 ppm and in the ^1H spectra as a singlet at 5.66-5.85 ppm (Table 2.2).

Table 2.2 NMR Chemical Shifts (δ) for the Characteristic Benzotriazole Carbons C-3a and C-7a, and Methylene Groups in Products 2.17 and 2.22

Prod.	$\delta_{\text{C}}(\text{C-3a})$	$\delta_{\text{C}}(\text{C-7a})$	$\delta_{\text{C}}(\text{CH}_2)$	$\delta_{\text{H}}(\text{CH}_2)$
2.17a	146.2	132.5	52.0	5.70
2.17b	146.2	132.6	52.1	5.70
2.22a	145.4	132.4	51.1	5.76
2.22b	143.1	132.5	51.4	5.66
2.22c	146.3	132.8	48.0	5.85

2.2.3 Displacement of Benzotriazole in 4-(Benzotriazol-1-ylmethyl)anilines

The benzotriazole group in 4-(benzotriazol-1-ylmethyl)anilines (2.17) or (2.22) was easily displaced by

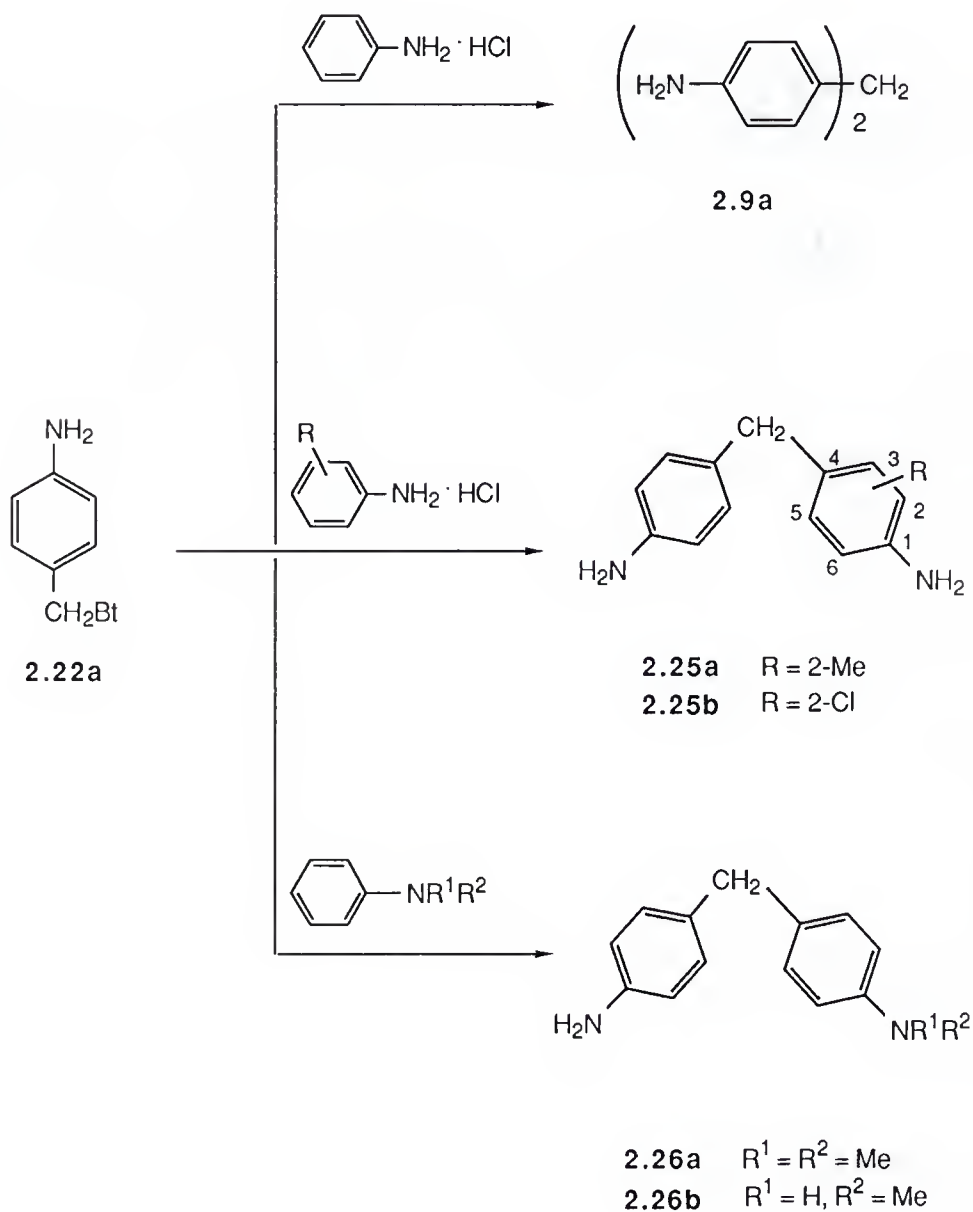
different types of anilines, as expected, to afford a series of 4,4'-methylenebisanilines. This type of displacement was assisted by the electron pair from the amino nitrogen.

Two types of reaction conditions have been utilized. One was to reflux a mixture of the benzotriazole adduct and the aniline in acetic acid. On work up, the solution was neutralized and then basified, thus removing the benzotriazole by-product as its anion and making isolation of the product easier. Under alternative reaction conditions, a mixture of the benzotriazole adduct and an aniline was heated with concentrated hydrochloric acid in 50% aqueous methanol, followed by neutralization. Thus, 4-(benzotriazol-1-ylmethyl)aniline (2.22a) was heated with arylamines to give symmetrical and unsymmetrical bis(4-aminoaryl)methanes 2.9 and 2.25, respectively. With N-substituted anilines, the mixed bis-anilines of type 2.26 were formed (Scheme 2.8).

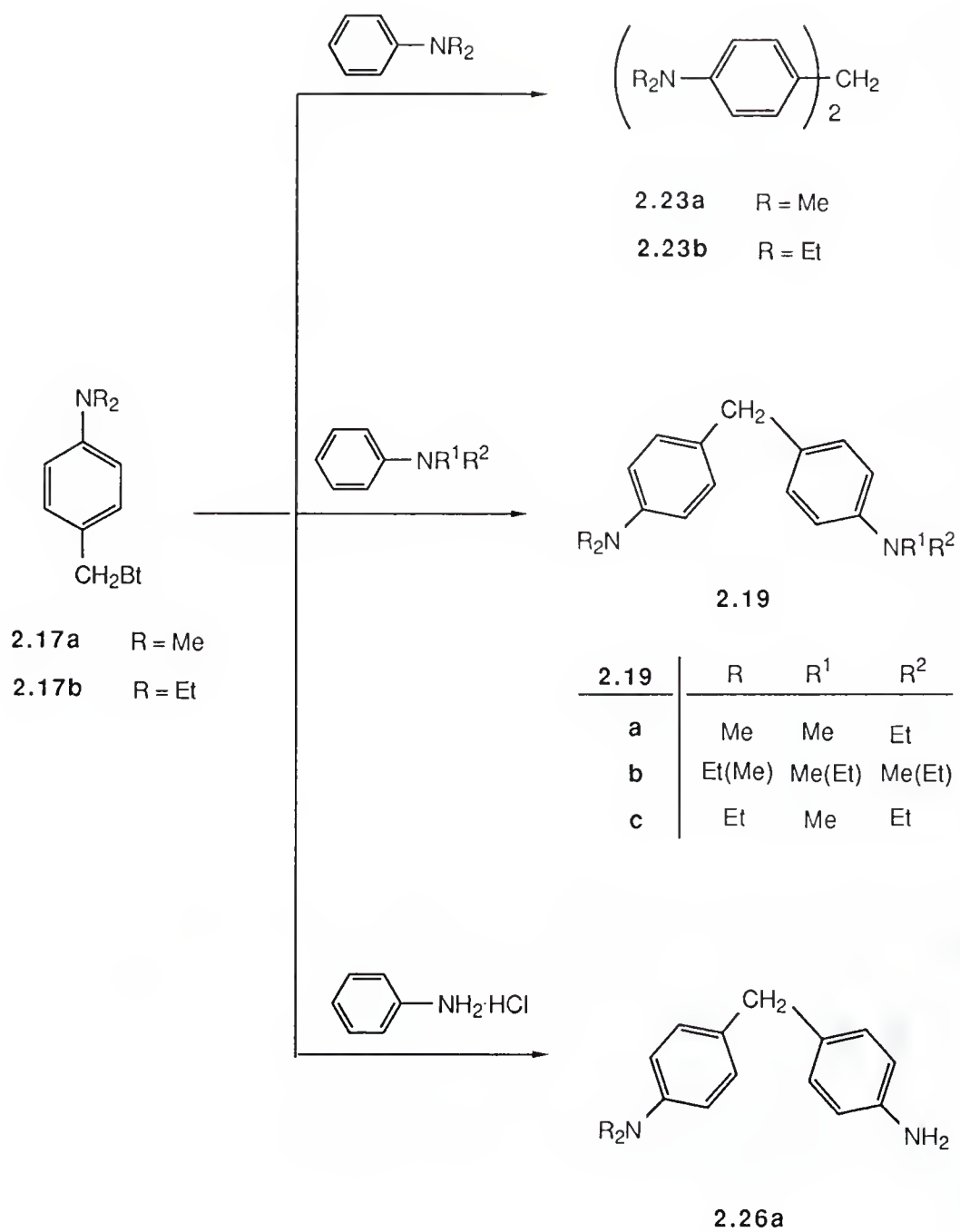
4-(Benzotriazol-1-ylmethyl)-N,N-dialkylanilines (2.17) reacted with N,N-dialkylanilines to give very high yields of the symmetrical 4,4'-methylenebis(N,N-dialkylanilines) (2.23) if the same N,N-dialkylaniline was used. When a different N,N-dialkylaniline was used, the unsymmetrical 4,4'-methylenebis(N,N,N',N'-tetraalkyl-anilines) (2.19) were obtained in excellent yields. Such unsymmetrical analogues have previously not been reported.

Thus this method provides a novel synthetic route to the unsymmetrical analogues of type 2.19 (Scheme 2.9).

Compound 2.17a also reacted with aniline hydrochloride to give compound 2.26a in 70% yield.



Scheme 2.8



Scheme 2.9

Table 2.3 Displacement of Benzotriazole

Prod.	Sub- strate	Method ^a	React. time (h)	Yield ^b (%)	M.p. (°C)
2.9a	2.22a	A	72	80	90-92
2.19a	2.17a	B	1	96	oil
2.19b	2.17a	B	1.5	99	oil
2.19b	2.17b	B	1	100	oil
2.19c	2.17b	B	2.5	96	oil
2.23a	2.17a	B	3	97	89-90 ^c
2.23a	2.15a	C	3	85	
2.23b	2.17b	B	3	90	43-44 ^d
2.23b	2.15b	C	3	95	
2.25a	2.22a	A	72	78	127-129 ^e
2.25b	2.22a	A	72	72	80-82
2.26a	2.22a	A	72	83	88-90 ^f
2.26a	2.17a	A	72	70	
2.26b	2.22a	A	72	66	58-60 ^g

^a Method A: The reactants were heated in 50% aqueous methanol solution.

Method B: The reactants were heated in acetic acid.

Method C: N,N-Dialkylaniline and 1-hydroxymethylbenzene were heated in acetic acid.

^b Isolated yields.

^c Lit. [87JCR(S)194] m.p. 88-89 °C.

^d Lit. [54MI1] m.p. 42-44 °C.

^e Lit. [80JCS(P1)1420] m.p. 127 °C.

^f Lit. [55MI1] m.p. 89-90 °C.

^g Lit. [80JCS(P1)1420] reported it as an oil.

The structures of these 4,4'-methylenebisanilines were confirmed by their spectral data and elemental analysis. Known compounds have been compared to those reported in the literature. All methylenebisanilines display the characteristic methylene singlets between δ 3.67–3.94 in the ^1H NMR spectra and the corresponding signals between δ 34.8–40.2 in the ^{13}C spectra. The upfield shift of both protons and carbons, compared to those of the benzotriazole adducts 2.17 and 2.22, indicated that the methylene group was connected to two phenyl rings (Table 2.4).

Table 2.4 ^1H and ^{13}C NMR Chemical Shifts (δ) for
Characteristic Methylene Groups in
4,4'-Methylenebisanilines

Prod.	$\delta_{\text{H}}(\text{CH}_2)$	$\delta_{\text{C}}(\text{CH}_2)$	Prod.	$\delta_{\text{H}}(\text{CH}_2)$	$\delta_{\text{C}}(\text{CH}_2)$
2.9a	3.74	40.0	2.19c	3.77	39.8
2.9b	3.68	39.5	2.23a	3.78	39.8
2.9c	3.94	34.8	2.23b	3.75	39.7
2.9d	3.72	40.2	2.25a	3.67	39.3
2.9e	3.68	34.9	2.25b	3.79	39.7
2.19a	3.79	39.8	2.26a	3.78	40.0
2.19b	3.78	39.8	2.26b	3.75	40.0

2.3 Conclusions

Bis(4-aminoaryl)methanes are prepared by the reaction of N-(benzotriazol-1-ylmethyl)arylamines with arylamine hydrochlorides in moderate to good yields. Methylene-bis(N,N-dialkylaniline)s are prepared by the reactions of 1-hydroxymethylbenzotriazole with N,N-dialkylanilines under acidic conditions. The intermediates 4-(benzotriazol-1-ylmethyl)anilines and their N,N-dialkyl analogs can be isolated and then used in reactions with different types of anilines allowing for the efficient preparation of both symmetrical and unsymmetrical methylenebis-anilines.

2.4 Experimental

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. ^1H NMR spectra were obtained on a Varian VXR 300 (300 MHz) spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained on a Varian VXR 300 (75 MHz) spectrometer, referring to the central signal of CDCl_3 (77.0 ppm) or DMSO-d_6 (39.5 ppm), respectively. CDCl_3 was used as the solvent for both ^1H and ^{13}C NMR spectra except where stated otherwise. Elemental analyses were performed using

a Carlo Erba 1106 elemental analyzer at the University of Florida, Department of Chemistry under the supervision of Dr. D.H. Powell.

Column chromatography was carried out on Alumina Basic (Brockman Activity I, 80-200 mesh, Fischer).

1-Hydroxymethylbenzotriazole (2.16) was prepared according to the modified literature procedure, m.p. 149-151 °C (lit. [52JA3868] m.p. 148-151 °C). The arylamine hydrochlorides 2.11 were prepared by mixing the corresponding arylamines and concentrated hydrochloric acid. N-(Benzotriazol-1-ylmethyl)arylamines (2.10) were prepared by the method of Katritzky et al. [87JCS(P1)799].

N-(Benzotriazol-1-ylmethyl)aniline (2.10a). M.p. 138-139 °C (lit. [90CJC446] m.p. 138-139 °C).

2-Chloro-N-(benzotriazole-1-ylmethyl)aniline (2.10b). Obtained as plates (recrystallized from methanol), m.p. 134-136 °C. ^1H NMR δ 6.31 (d, J = 6.6 Hz, 2 H), 6.70 (t, J = 7.0 Hz, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.26-7.63 (m, 5 H), 8.1-8.3 (m, 2 H); ^{13}C NMR δ 56.6, 111.3, 112.2, 118.3, 118.6, 119.1, 124.0, 127.2, 127.8, 129.3, 132.2, 141.6, 145.5.

Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{ClN}_4$: C, 60.35; H, 4.29; N, 21.66. Found: c, 60.75; H, 4.28; N, 21.97.

3-Chloro-N-(benzotriazol-1-ylmethyl)aniline (2.10c). M.p. 174-176 °C (lit. [90CJC446] m.p. 176 °C).

2-Methyl-N-(benzotriazol-1-ylmethyl)aniline (2.10d).

m.p. 146-147.5 °C (lit. [90CJC446] m.p. 146 °C).

3-Methyl-N-(benzotriazol-1-ylmethyl)aniline (2.10e).

Obtained as needles (recrystallized from ethanol), m.p. 156-157 °C. ^1H NMR δ 2.15 (s, 3 H), 6.15 (d, J = 7.5 Hz, 2 H), 6.43 (d, J = 7.5 Hz, 1 H), 6.70 (t, J = 7.0 Hz, 2 H), 6.90 (t, J = 7.0 Hz, 1 H), 7.25-7.55 (m, 3 H), 8.0-8.1 (m, 2 H); ^{13}C NMR δ 21.2, 57.0, 109.9, 111.2, 113.6, 118.7, 119.0, 123.9, 127.0, 128.9, 132.2, 138.1, 145.5, 145.7.

Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.49; H, 5.89; N, 23.65.

2.4.1 General Procedure for the Preparation of Bis(4-aminoaryl)methanes (2.9) using N-(Benzotriazol-1-ylmethyl)arylamines

To a stirred solution of N-(benzotriazol-1-ylmethyl)arylamine (2.10) (20 mmol) in methanol (30 ml) was added a solution of the corresponding arylamine hydrochloride (2.11) (40 mmol) dissolved in water (30 ml). The resulting mixture was heated under reflux for 3 h, hydrolyzed with aqueous potassium hydroxide (1 M; 50 ml) and extracted with diethyl ether (3 $\times$ 100 ml). The organic layer was dried (MgSO_4), the solvent evaporated and the excess arylamine distilled off under reduced pressure, the residue purified as described for each individual compound. Yields and melting points of 2.9a-e are given in Table 2.1.

Bis(4-aminophenyl)methane (2.9a). Obtained as needles (recrystallized from hexane/EtOAc). ^1H NMR δ 3.50 (broad, 4 H, $-\text{NH}_2$), 3.74 (s, 2 H, $-\text{CH}_2-$), 6.56 (d, $J = 8.0$ Hz, 4 H), 6.92 (d, $J = 8.0$ Hz, 4 H); ^{13}C NMR δ 40.0 ($-\text{CH}_2-$), 115.1, 129.5, 131.8, 144.2.

Reaction of 2.10b with 2-chloroaniline hydrochloride (2.11b). The crude product was chromatographed from hexane/EtOAc, 2:1, v/v, to give bis(4-amino-3-chlorophenyl)methane (2.9b) (44%) as needles and 4-(benzotriazol-1-ylmethyl)-2-chloroaniline (2.22b) (26%) as microcrystals.

Bis(4-amino-3-chlorophenyl)methane (2.9b). ^1H NMR δ 3.68 (s, 2 H, $-\text{CH}_2-$), 3.91 (broad, 4 H, $-\text{NH}_2$), 6.63-6.66 (m, 2 H), 6.81-6.84 (m, 2 H), 7.01-7.02 (m, 2 H); ^{13}C NMR δ 39.5 ($-\text{CH}_2-$), 115.9, 119.2, 128.0, 129.4, 132.1, 141.0.

4-(Benzotriazol-1-ylmethyl)-2-chloroaniline (2.22b). M.p. 106-109°C. ^1H NMR δ 4.15 (broad, 2 H, $-\text{NH}_2$), 5.66 (s, 2 H, $-\text{CH}_2-$), 6.66 (d, $J = 8$ Hz, 1 H), 6.96-6.97 (m, 1 H), 7.21-7.39 (m, 4 H), 8.01-8.05 (m, 1 H); ^{13}C NMR δ 51.4 ($-\text{CH}_2-$), 109.7, 115.8, 119.1, 119.9, 123.8, 124.9, 127.2, 127.3, 128.8, 132.5, 143.1, 146.2.

Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{ClN}_4$: C, 60.35; H, 4.29; N, 21.66. Found: C, 60.65; H, 4.30; N, 21.41.

Reaction of 2.10c with 3-chloroaniline hydrochloride (2.11c). The crude product was chromatographed from hexane/EtOAc, 2:1, v/v, to give bis(4-amino-2-chlorophenyl)methane (2.9c) (32%) as microcrystals and 4-(benzotriazol-1-ylmethyl)-3-chloroaniline (2.22c) (7%) as needles.

Bis(4-amino-2-chlorophenyl)methane (2.9c). ^1H NMR δ 3.62 (broad, 4 H, $-\text{NH}_2$), 3.94 (s, 2 H, $-\text{CH}_2-$), 6.44–6.48 (m, 2 H), 6.70 (d, $J = 2.0$ Hz, 2 H), 6.78 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR δ 34.8 ($-\text{CH}_2-$), 113.7, 115.6, 127.3, 131.1, 134.5, 145.7.

4-(Benzotriazol-1-yl)-3-chloroaniline (2.22c). M.p. 136–138°C. ^1H NMR δ 3.82 (broad, 2 H, $-\text{NH}_2$), 5.85 (s, 2 H, $-\text{CH}_2-$), 6.46 (dd, $J = 8.0, 2.0$ Hz, 1 H), 6.71 (d, $J = 2.0$ Hz, 1 H), 6.93 (d, $J = 8.0$ Hz, 1 H), 7.26–7.46 (m, 3 H), 8.02–8.07 (m, 1 H); ^{13}C NMR δ 49.0 ($-\text{CH}_2-$), 109.9, 113.9, 115.3, 119.9, 121.5, 123.8, 127.3, 130.9, 133.9, 146.2, 147.8.

Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{ClN}_4$: C, 60.35; H, 4.29; N, 21.66; Found: C, 60.04; H, 4.29; N, 21.56.

Bis(4-amino-3-methylphenyl)methane (2.9d). Obtained as plates (recrystallized from hexane/EtOAc). ^1H NMR δ 2.10 (s, 6H, $-\text{CH}_3$), 3.46 (broad, 4 H, $-\text{NH}_2$), 3.68 (s, 2 H,

-CH₂-), 6.56 (d, $J = 8.0$ Hz, 2 H), 6.82-6.85 (m, 4H); ¹³C NMR δ 17.3 (-CH₃), 40.2 (-CH₂-), 115.0, 122.4, 127.1, 130.8, 132.1, 142.4.

Bis(4-amino-2-methylphenyl)methane (2.9e). Obtained as microcrystals (column chromatography from hexane/EtOAc, 2:1, v/v). ¹H NMR δ 2.15 (s, 6H, -CH₃), 3.49 (broad, 4 H, -NH₂), 3.68 (s, 2 H, -CH₂-), 6.41-6.43 (m, 2 H), 6.51 (d, $J = 2.0$ Hz, 2 H), 6.66 (d, $J = 8.0$ Hz, 2 H); ¹³C NMR δ 19.5 (-CH₃), 34.9 (-CH₂-), 112.6, 117.0, 129.0, 129.8, 137.3, 144.3.

Procedure for the Rearrangement of N-(Benzotriazol-1-ylmethyl)aniline (2.10a). To a stirred solution of N-(benzotriazol-1-ylmethyl)aniline (2.10a) (1.12 g, 5 mmol) in methanol (30 ml) under reflux was added dilute hydrochloric acid (3%; 30 ml). The resulting mixture was heated under reflux for 4 h and then hydrolyzed with aqueous potassium hydroxide (1 M; 50 ml). The product was extracted with diethyl ether (3 x 60 ml) and the organic extracts dried (MgSO₄). Evaporation of the solvent followed by recrystallization from toluene gave 4-(benzotriazol-1-ylmethyl)aniline (2.22a) (0.52 g, 59%) as needles, m.p. 144-146 °C. ¹H NMR (DMSO-d₆) δ 5.20 (broad, 2 H, -NH₂), 5.75 (s, 2 H, -CH₂-), 6.50 (d, $J = 8.0$ Hz, 2 H), 7.10 (d, $J = 8.0$ Hz, 2 H), 7.37 (t, $J = 7.0$ Hz,

1 H), 7.50 (t, $J = 8.0$ Hz, 1 H), 7.80 (d, $J = 8.0$, 1 H), 8.04 (d, $J = 8.0$ Hz, 1 H); ^{13}C NMR (DMSO- d_6) δ 51.2 ($-\text{CH}_2-$), 110.9, 113.8, 119.1, 122.3, 123.8, 127.1, 129.1, 132.4, 145.4, 148.7.

Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_4$: C, 69.62; H, 5.39; N, 24.98; Found: C, 69.68; H, 5.50; N, 24.91.

2.4.2 General Procedure for the Preparation of 4-(Benzotriazol-1-ylmethyl)anilines

Method (A). A mixture of *N,N*-dialkylaniline or aniline hydrochloride (0.0385 mol) and 1-hydroxymethylbenzotriazole (5.74 g, 0.0385 mol) in acetic acid (25 ml) was heated under reflux for 5 min and then poured into ice-water (200 ml). The resulting solution was rendered basic with aqueous sodium hydroxide (50%; 10 ml), extracted with diethyl ether (3 $\times$ 100 ml) and the ethereal solution dried (MgSO_4). Evaporation of the solvent afforded products which were purified as described for each individual compound.

Method (B). A mixture of *N,N*-dimethylaniline (6.06 g, 0.05 mol) and concentrated hydrochloric acid (4.3 ml, 0.05 mol) was heated under reflux for 1 h. A solution of 1-hydroxymethylbenzotriazole (7.46 g, 0.05 mol) in propanol (25 ml) was then added, the mixture heated under reflux for 7.5 h and then stirred at room temperature overnight. The solvent was evaporated to give a sticky

oil, to which was added a sodium hydroxide solution (15%; 30 ml) and a small amount of diethyl ether. The white precipitate obtained was collected and washed with a small amount of diethyl ether to give pure 2.17a (5.75 g, 46%). The residue was extracted with diethyl ether (3 x 50 ml) and dried (MgSO₄). Evaporation of the solvent gave 4,4'-methylenebis(N,N-dimethylaniline) (2.23a) (1.90 g, 30%).

4-(Benzotriazol-1-ylmethyl)aniline (2.22a). The precipitate obtained after rendering the solution basic (by method (A)) was collected and recrystallized from toluene to give 2.22a in 60% yield. It is identical in all aspects with the sample prepared earlier.

Reaction of N,N-dimethylaniline with 1-hydroxymethyl-benzotriazole. The crude product from the reaction by method (A) was boiled with hexane. The insoluble solid was filtered and recrystallized from methanol to give 4-(benzotriazol-1-ylmethyl)-N,N-dimethylaniline (2.17a) (19%) as needles. Evaporation of hexane followed by recrystallization from petroleum ether gave 4,4'-methylenebis(N,N-dimethylaniline) (2.23a) (80%) as plates. A reaction by method (B) gave 46% of 2.17a along with 30% of 2.23a.

4-(Benzotriazol-1-ylmethyl)-N,N-dimethylaniline

(2.17a). M.p. 167-168.5 °C. ^1H NMR δ 2.92 (s, 6 H, N-CH $_3$), 5.74 (s, 2 H, -CH $_2$ -), 6.62 (d, J = 8.8 Hz, 2 H), 7.16-7.35 (m, 5 H), 8.00 (d, J = 8.0 Hz, 1 H); ^{13}C NMR δ 40.2 (N-CH $_3$), 52.0 (-CH $_2$ -), 110.0, 112.7, 119.7, 121.8, 123.6, 126.9, 128.8, 132.5, 146.2, 150.3.

Anal. Calcd for C $_{15}$ H $_{16}$ N $_4$: C, 71.40; H, 6.39; N, 22.20. Found: C, 71.34; H, 6.44; N, 22.18.

4,4'-Methylenebis(N,N-dimethylaniline) (2.23a).

^1H NMR δ 2.90 (s, 12 H, N-CH $_3$), 3.80 (s, 2 H, -CH $_2$ -), 6.68 (d, J = 8.0 Hz, 4 H), 7.05 (d, J = 8.0 Hz, 4 H); ^{13}C NMR δ 39.8 (-CH $_2$ -), 40.8 (N-CH $_3$), 112.9, 129.3, 130.2, 146.9.

Reaction of N,N-diethylaniline with 1-hydroxymethyl-benzotriazole. The precipitate after rendering the reaction solution basic (by method (A)) was collected and recrystallized from hexane/benzene to give 4-(benzotriazol-1-ylmethyl)-N,N-diethylaniline (2.17b) (14%) as prisms. The solution was extracted with diethyl ether (3 $\times$ 100 ml) and the ethereal solution dried (MgSO $_4$). Evaporation of the solvent gave an oil, which upon stay for several days crystallized to give 4,4'-methylenebis(N,N-diethylaniline) (2.23b) (52%) as plates.

4-(Benzotriazol-1-ylmethyl)-N,N-diethylaniline

(2.17b). M.p. 104-106 °C. ^1H NMR δ 1.11 (t, J = 7.0 Hz, 6 H, $\text{NCH}_2\text{-CH}_3$), 3.28 (q, J = 7.0 Hz, 4 H, $\text{N-CH}_2\text{CH}_3$), 5.70 (s, 2 H, $\text{-CH}_2\text{-}$), 6.60 (d, J = 8.8 Hz, 2 H), 7.16 (d, J = 8.8 Hz, 2 H), 7.29-7.40 (m, 3 H), 8.02 (d, J = 8.0 Hz, 1 H); ^{13}C NMR δ 12.4 ($\text{NCH}_2\text{-CH}_3$), 44.2 ($\text{N-CH}_2\text{CH}_3$), 52.2 ($\text{-CH}_2\text{-}$), 110.1, 111.5, 119.7, 120.6, 123.7, 127.0, 129.1, 132.6, 146.1, 147.7.

Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_4$: C, 72.83; H, 7.19; N, 19.98. Found: C, 72.84; H, 7.24; N, 20.19.

4,4'-Methylenebis(N,N-diethylaniline) (2.23b). ^1H NMR

δ 1.10 (t, J = 7.0 Hz, 12 H, $\text{NCH}_2\text{-CH}_3$), 3.27 (q, J = 7.0 Hz, 8 H, $\text{N-CH}_2\text{CH}_3$), 3.76 (s, 2 H, $\text{-CH}_2\text{-}$), 6.60 (d, J = 8.7 Hz, 4 H), 7.00 (d, J = 8.7 Hz, 4 H); ^{13}C δ 12.5 ($\text{NCH}_2\text{-CH}_3$), 39.7 ($\text{-CH}_2\text{-}$), 44.3 ($\text{N-CH}_2\text{CH}_3$), 112.1, 129.1, 129.5, 146.0.

2.4.3 General Procedure for the Displacement of Benzotriazole by Anilines

Method (A). To a stirred solution of 4-(benzotriazol-1-ylmethyl)-N,N-dialkylanilines (2.17) (or with alkyl = H; 2.22) (5 mmol) in methanol (30 ml) under reflux was added a mixture of the appropriate aniline (10 mmol) and dilute hydrochloric acid (10%; 30 ml). The resulting mixture was then heated under reflux for 3 days, hydrolyzed with aqueous potassium hydroxide (1 M; 50 ml) and extracted

with diethyl ether (3 × 100 ml). The organic layer was dried (MgSO_4) and the solvent evaporated, the residue purified as described for each individual compound.

Method (B). A mixture of N,N-dialkylaniline (0.01 mol) and 4-(benzotriazol-1-ylmethyl)-N,N-dialkylaniline (2.17) (0.01 mol) in acetic acid (25 ml) was heated under reflux for the appropriate time (see Table 2.3), then poured into ice-water (50 ml). The resulting solution was rendered basic with aqueous sodium hydroxide (50%; 40 ml), extracted with diethyl ether (3 × 60 ml) and the ethereal solution dried (MgSO_4). The solvent was evaporated to give the essentially pure product.

Method (C). A mixture of N,N-dialkylaniline (0.081 mol) and 1-hydroxymethylbenzotriazole (5.74 g, 0.0385 mol) in acetic acid (25 ml) was heated under reflux for 3 h and then poured into ice-water (60 ml). The resulting solution was rendered basic with aqueous sodium hydroxide (50%; 40 ml), extracted with diethyl ether (3 × 60 ml) and the ethereal solution dried (MgSO_4). The solvent was evaporated to give the essentially pure product.

Physical data of the products, yields, and methods of the preparation are given in Table 2.3.

Bis(4-aminophenyl)methane (2.9a). Obtained by method (A) from 2.22a and aniline hydrochloride (column chromatography from hexane/EtOAc, 2:1, v/v). It is identical in all aspects with the sample prepared earlier.

4,4'-Methylenebis(N,N,N'-trimethyl-N'-ethylaniline)

(2.19a). Obtained by method (B) from N-methyl-N-ethylaniline and 2.17a as an oil. ^1H NMR δ 1.06 (t, J = 7.0 Hz, 3 H, $\text{NCH}_2\text{-CH}_3$), 2.82 (s, 3 H, $\text{CH}_3\text{CH}_2\text{N-CH}_3$), 2.85 (s, 6 H, $\text{N(CH}_3)_2$), 3.31 (q, J = 7.0 Hz, 2 H, $\text{N-CH}_2\text{CH}_3$), 3.78 (s, 2 H, $\text{-CH}_2\text{-}$), 6.63-6.69 (m, 4 H), 7.02-7.07 (m, 4 H); ^{13}C NMR δ 11.1 ($\text{NCH}_2\text{-CH}_3$), 37.5 ($\text{CH}_3\text{-NCH}_2\text{CH}_3$), 39.8 ($\text{-CH}_2\text{-}$), 40.8 ($\text{N(CH}_3)_2$), 46.9 ($\text{N-CH}_2\text{CH}_3$), 112.6, 112.9, 129.3, 129.4, 129.6, 130.3, 147.3, 148.9.

Anal. Calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2$: C, 80.55; H, 9.01. Found: C, 80.53; H, 9.04.

4,4'-Methylenebis(N,N-dimethyl-N',N'-diethylaniline)

(2.19b). Obtained by method (B) from 2.17a and N,N-diethylaniline, or from 2.17b and N,N-dimethylaniline, as an oil. ^1H NMR δ 1.10 (t, J = 7.0 Hz, 6 H, NCH_2CH_3), 2.85 (s, 6 H, N-CH_3), 3.26 (q, J = 7.0 Hz, 4 H, $\text{N-CH}_2\text{CH}_3$), 3.78 (s, 2 H, $\text{-CH}_2\text{-}$), 6.63-6.69 (m, 4 H), 7.02-7.07 (m, 4 H); ^{13}C NMR δ 12.5 ($\text{N-CH}_2\text{CH}_3$), 39.8 ($\text{-CH}_2\text{-}$), 40.8 (N-CH_3), 44.3 ($\text{N-CH}_2\text{CH}_3$), 112.1, 112.9, 128.9, 129.3, 129.4, 130.3, 146.0, 149.0.

Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{N}_2$: C, 80.80; H, 9.28. Found: C, 80.58; H, 9.26.

4,4'-Methylenebis(N,N,N'-triethyl-N'-methylaniline)

(2.19c). Obtained by method (B) from N-methyl-N-

ethylaniline and 2.17b as an oil. ^1H NMR δ 1.05–1.13 (m, 9 H, $\text{N}(\text{CH}_2\text{CH}_3)_2 + \text{CH}_3\text{NCH}_3\text{--CH}_3$), 2.83 (s, 3 H, $\text{CH}_3\text{--NCH}_2\text{CH}_3$), 3.27–3.31 (m, 6 H, $\text{CH}_3\text{NCH}_2\text{CH}_3 + \text{N}(\text{CH}_2\text{CH}_3)_2$), 3.78 (s, 2 H, $\text{--CH}_2\text{--}$), 6.59–6.65 (m, 4 H), 7.00–7.03 (m, 4 H); ^{13}C NMR δ 11.1 ($\text{CH}_3\text{NCH}_2\text{--CH}_3$), 12.5 ($\text{N}(\text{CH}_2\text{CH}_3)_2$), 37.5 ($\text{--CH}_2\text{--}$), 39.8 ($\text{CH}_3\text{--NCH}_2\text{CH}_3$), 44.4 ($\text{CH}_3\text{N--CH}_2\text{CH}_3$), 47.0 ($\text{N}(\text{CH}_2\text{CH}_3)_2$), 112.2, 112.3, 112.7, 129.1, 129.4, 129.8, 146.0, 147.4.

Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2$: C, 81.03; H, 9.52. Found: C, 81.07; H, 9.52.

4,4'-Methylenebis(N,N-dimethylaniline) (2.23a).

Obtained by method (B) from N,N-dimethylaniline and 2.17a, or by method (C) from N,N-dimethylaniline and 2.16. It is identical in all aspects with the sample prepared earlier.

4,4'-Methylenebis(N,N-diethylaniline) (2.23b).

Obtained by method (B) from N,N-diethylaniline and 2.17b, or by method (C) from N,N-diethylaniline and 2.16. It is identical in all aspects with the sample prepared earlier.

4-(4-Aminobenzyl)-2-methylaniline (2.25a). Obtained by method (A) from 2-methylaniline hydrochloride and 2.22a as plates (column chromatography from hexane/EtOAc, 1:1, v/v). ^1H NMR δ 2.08 (s, 3 H, --CH_3), 3.67 (s, 2 H, $\text{--CH}_2\text{--}$), 3.86 (broad, 4 H, --NH_2), 6.5–6.6 (m, 3 H), 6.7–6.8 (m, 4 H); ^{13}C NMR δ 16.5 (--CH_3), 39.3 ($\text{--CH}_2\text{--}$), 113.9, 114.0, 121.0, 126.0, 128.4, 129.7, 130.3, 130.4, 142.1, 144.1.

4-(4-Aminobenzyl)-2-chloroaniline (2.25b). Obtained by method (A) from 2-chloroaniline hydrochloride and 2.22a as microcrystals (column chromatography from hexane/EtOAc, 2:1, v/v). ^1H NMR δ 3.50 (broad, 2 H, $-\text{NH}_2$), 3.70 (s, 2 H, $-\text{CH}_2-$), 3.90 (broad, 2 H, $-\text{NH}_2$), 6.5-6.6 (m, 3 H), 6.83 (dd, $J = 8.0, 2.0$ Hz, 1 H), 6.90-6.93 (m, 2 H), 7.02 (d, $J = 2.0$ Hz, 1 H); ^{13}C NMR δ 39.7 ($-\text{CH}_2-$), 115.2, 115.8, 119.1, 127.9, 129.3, 129.5, 131.0, 132.8, 140.7, 144.4.

Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{ClN}_2$: C, 67.10; H, 5.63; N, 12.04. Found: C, 67.17; H, 5.66; N, 12.03.

4-(4-Aminobenzyl)-N,N-dimethylaniline (2.26a). Obtained by method (A) from aniline hydrochloride and 2.17a (column chromatography from hexane/EtOAc, 1:1, v/v), or by method (A) from 2.22a and N,N-dimethylaniline (recrystallized from hexane) as microcrystals. ^1H NMR δ 2.88 (s, 6 H, $\text{N}-\text{CH}_3$), 3.50 (broad, 2 H, $-\text{NH}_2$), 3.77 (s, 2 H, $-\text{CH}_2-$), 6.57 (d, $J = 8.0$ Hz, 2 H), 6.66 (d, $J = 8.0$ Hz, 2 H), 6.94 (d, $J = 8.0$ Hz, 2 H), 7.02 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR δ 40.0 ($-\text{CH}_2-$), 40.8 ($\text{N}-\text{CH}_3$), 112.9, 115.2, 129.3, 129.5, 130.0, 132.0, 144.2, 149.0.

4-(4-Aminobenzyl)-N-methylaniline (2.26b). Obtained by method (A) from 2.22a and N-methylaniline as microcrystals (column chromatography from hexane/EtOAc, 1:2, v/v). ^1H NMR δ 2.74 (s, 3 H, $\text{N}-\text{CH}_3$), 3.45 (broad, 3

H, $-\text{NH}_2 + \text{CH}_3-\text{NH}$), 3.75 (s, 2 H, $-\text{CH}_2-$), 6.4-6.6 (m, 4 H), 6.9-7.0 (m, 4 H); ^{13}C NMR δ 30.8 ($\text{N}-\text{CH}_3$), 40.0 ($-\text{CH}_2-$), 112.4, 115.1, 129.37, 129.43, 130.5, 132.0, 144.1, 147.4.

Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 78.83; H, 7.61; N, 13.15.

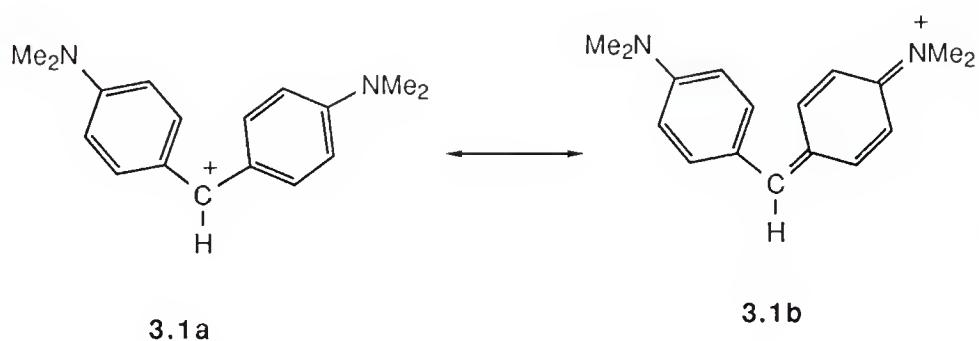
CHAPTER III
BENZOTRIAZOLE AS A SYNTHETIC AUXILIARY:
ALTERNATIVE SYNTHESIS OF LEUCO DYESTUFFS

3.1 Introduction

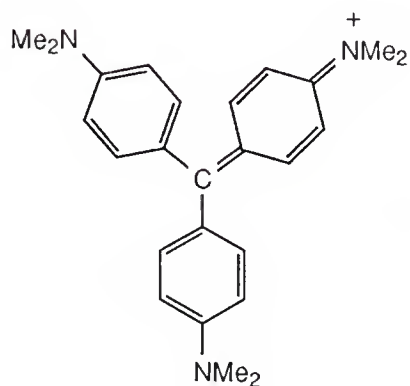
3.1.1 Leuco Dyes

A "leuco dye" is generally defined as a compound which yields a dye on oxidation. Di- and tri-arylmethanes containing electron-donating substituents such as amino groups and the hydroxy group (as well as its conjugate base) in the ortho or para positions are leuco dyes. Hydride abstraction by oxidizing agents gives colored cations. Some of the common dyes of this type are Michler's hydrol (3.1), Crystal Violet (3.2) and Malachite Green (3.3). Lead dioxide has been the traditional oxidizing agent. However, the search for lead-free processes has given rise to the use of other oxidizing agents such as chloranil, or air in the presence of catalytic amounts of cobalt or iron chelates. The general method of synthesis of these leuco bases involves the treatment of a one carbon electrophilic reagent (formaldehyde, chloroform, etc) with arene nucleophiles (usually substituted by electron donors such as NR_2 , NHR , NH_2 , OH) via an $\text{S}_{\text{E}}2$ mechanism [87MI5]. Scheme 3.1

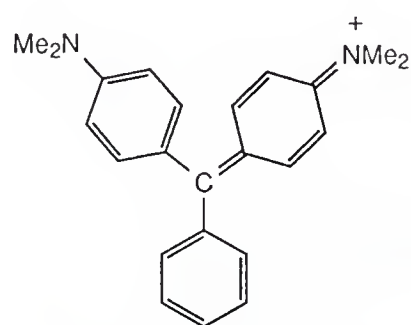
illustrates in general the typical methods for the preparation of this type of leuco base by demonstrating three different pathways for the synthesis of Crystal Violet [87MI5].



Michler's hydrol

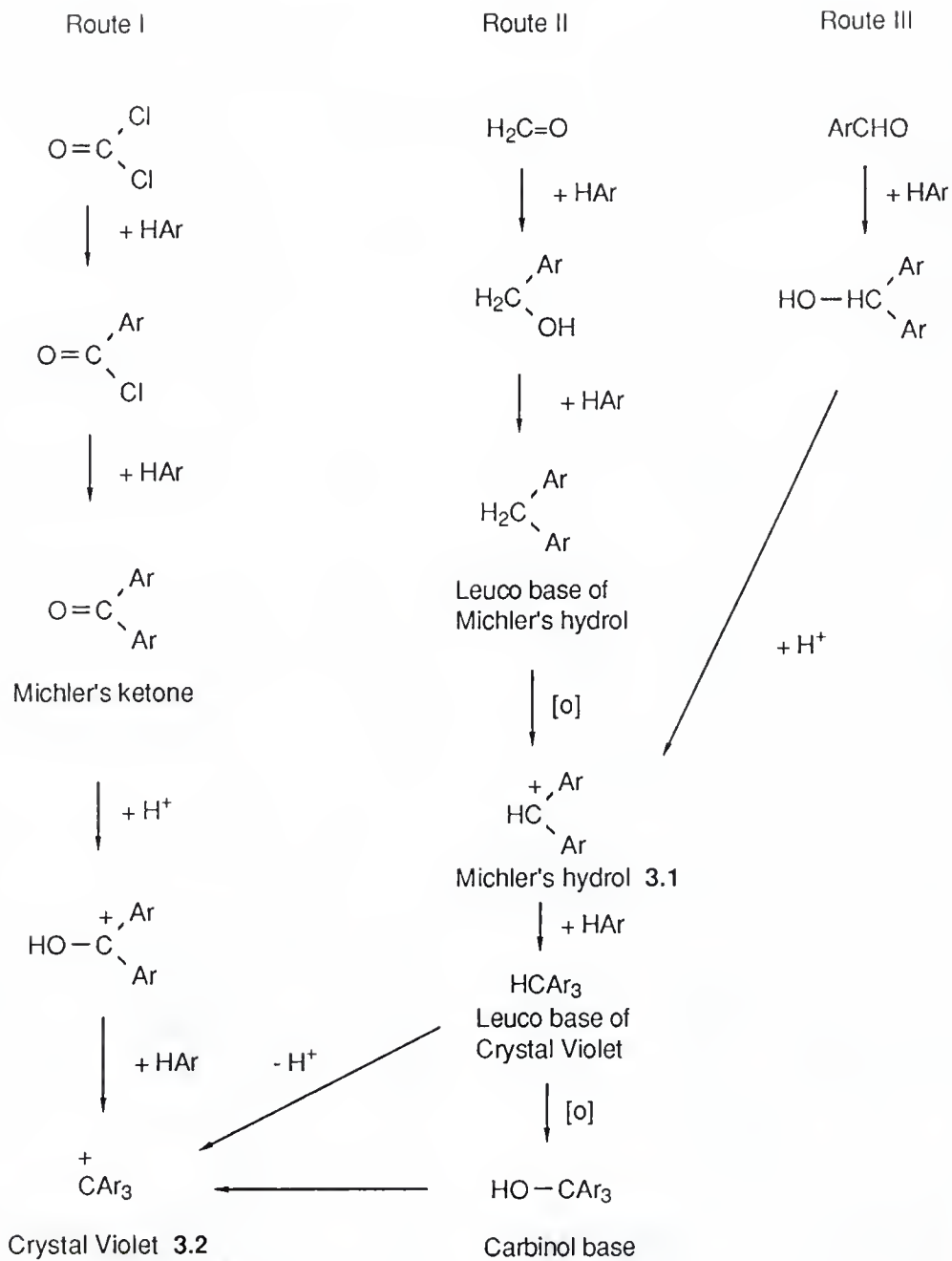


Crystal Violet



Malachite Green

Figure 3.1 Triarylmethane Dyes



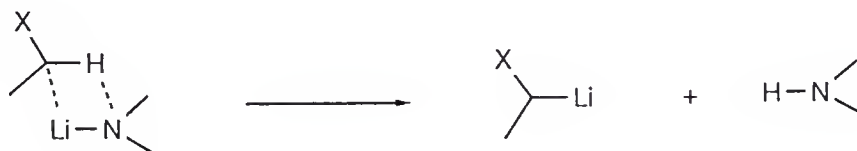
Scheme 3.1

A large number of vinylogous di- and tri-arylmethane dyes including a few heteroaromatic analogs have been described in the literature [52MI1, 76JOC870, 81MI1]. Among the hetarylmethane derivatives, Naef [81MI1] has synthesized trihetaryl dyes in yields of 20-85% by treatment of unsymmetrical dihetaryl ketones with 1,2-dimethylindole in the presence of phosphorus oxychloride. However, the cationic dyes were directly formed without isolation of the leuco bases. Other hetaryl dyes that have been prepared are diindolylpyridylmethanes [76JOC870] which afford colored compounds upon proton abstraction and hence cannot be considered as leuco dyes.

3.1.2 Overview on the Formation of α -Heterocarbanions and Activation of α -Methylene Groups by a Heterocyclic Moiety

Metalation reactions have long been known and have been reviewed by Gilman and Morton [54OR258] and more recently by Gschwend and Rodriguez [79OR1]. The term "metalation" in general and "lithiation" in particular, represents proton abstraction by a metal or lithium. Research efforts in this area have been dedicated to the search for new functional groups that promote lithiation, elaboration of novel heterocyclic and olefinic substrates as metalable species, recognition of new types of lithiating agents, and to the investigation of the mechanism of metalation.

Many lithiating reagents have been developed over the years and can be divided into two types. The first type, lithium alkyls and lithium aryls, are oligomers of varying complexity in solution [53JA3278, 62JOC1667, 64JA2076, 65MI2, 70JA4664, 73JOM1, 74JOM327, 76JOC3653]. The electron-deficient lithium can coordinate with the solvent to form aggregates. Kinetically, these reagents become more basic as the aggregate size diminishes. The second type includes butyllithium/amine complexes and lithium dialkylamides. It has been found [59CB192, 60AG91] that lithium dialkylamides are generally more effective metalating agents than the thermodynamically more basic lithium alkyls and lithium aryls. This is explained by the increased kinetic basicity due to the availability of a free electron pair permitting the formation of a four-membered transition state (Scheme 3.2).



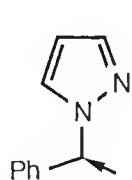
Scheme 3.2

Lithiation on a carbon adjacent to a heteroatom has become an increasingly important tool in synthetic

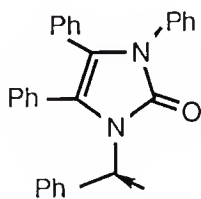
chemistry [69CRV693, 70MI1, 73MI1, 74MI1, 74MI2]. The presence of a heteroatom has both stabilization and destabilization effects on an α -carbanion. Formation of the negative charge is disfavored in cases where the adjacent heteroatom carries an electron pair (nitrogen or oxygen). Such atoms destabilize the carbanionic center. On the other hand, the inductive and resonance effects greatly increase the acidity of the adjacent carbon-hydrogen bond, thus making alpha lithiations facile [66JA943, 72ACR102, 75JA2209, 76JA5435, 76JA7498, 77JA5633, 78JA1604].

Much work has been done concerning activation of the methylene protons alpha to a nitrogen incorporated in a five-membered heterocyclic ring such as an N-alkylpyrazole [83T2023, 83T4133]. Metalation of N-alkyl heterocycles usually results in the replacement of a ring proton, although in some cases mixtures are obtained [53JA375, 71CJC2139, 72JOC215, 73CB2815, 76JOC163, 83T2023, 87JCS(P1)775]. Therefore in order to provide better regioselectivity at the α -C, other carbanion stabilizing substituents must be introduced. An aryl substituent has been used successfully to facilitate lithiation in N-benzylpyrazole (3.4) [83T2023], in N-benzyl-3,4,5-triphenyl-1,3-dihydroimidazol-2-one (3.5) [82JCR(S)26], in N-benzylimidazole (3.6) [74JOC1374, 84JCS(P1)481], and in N-arylmethylimidazoles [85S302]. Other activating groups include a second nitrogen-linked heterocyclic ring as seen

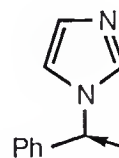
in methylenebispyrazoles (3.7) [83T4133], and in *p*-(bisbenzotriazol-1-ylmethyl)toluene (3.8) [87JCS(P1)819]; sulfur moieties such as phenylthio in 1-(phenylthiomethyl)benzimidazole (3.9) [87JCS(P1)775], in 9-(phenylthiomethyl)carbazole (3.10) [85JOC1351], and in 1-(phenylthiomethyl)benzotriazole (3.11) [87JCS(P1)781].



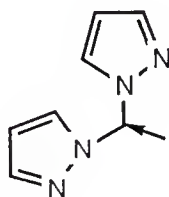
3.4



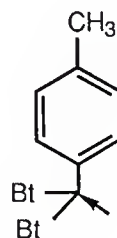
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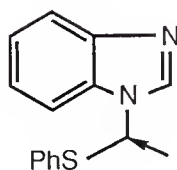
3.6



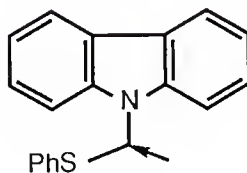
3.7



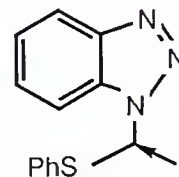
3.8



3.9



3.10



3.11

Bt = benzotriazol-1-yl

Figure 3.2 Activation and Lithiation of α -Heterocyclic Compounds

3.1.3 Aim of the work

In Chapter II, we have shown that aniline and N,N-dialkylanilines are readily alkylated by 1-hydroxymethylbenzotriazole to give 4-(benzotriazol-1-ylmethyl)anilines (3.12). Subsequent displacements of the benzotriazole group by arylamines or N,N-dialkylanilines give either symmetrical or unsymmetrical 4,4'-methylenebis(N,N,N',N'-tetraalkylanilines) (3.13).

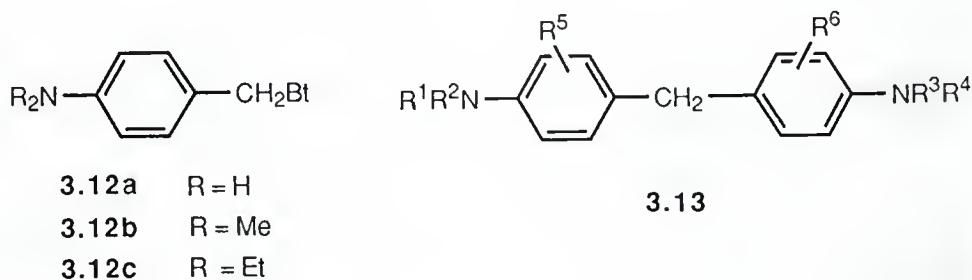


Figure 3.3 4-(Benzotriazol-1-ylmethyl)anilines and 4,4'-Methylenebis(anilines)

Compounds of type 3.13 have found numerous applications in industry. They are used as curing agents for epoxy resins and urethane elastomers, as intermediates in the preparation of polyurethanes, in the synthesis of polyamides and in the production of dyes and recording materials (For references, see section 2.1.1 in Chapter II). Modification of the molecule, such as by interchanging an aryl ring with a heterocyclic ring, or by introducing a functional group onto the methylene carbon,

should diversify the properties of these materials and perhaps widen their synthetic applications.

N-Benzylbenzotriazole has been shown to undergo lithiation at the benzylic carbon atom [90MI1]. Although N,N-dimethylaniline and 4,4'-methylenebis(N,N-dimethylaniline) both undergo ortho-metalation (due to chelation effects) [66JOC2047, 79JOC237], it was anticipated that the electron withdrawing nature of the benzotriazolyl moiety could direct the lithiation towards the benzylic position in derivatives of type 3.12. The benzotriazole group could then be displaced by nucleophiles.

The objective of the project was to investigate the displacement of benzotriazole by potential nucleophiles, other than anilines, thus preparing methylene derivatives with two different aromatic substituents. On the other hand, introduction of functional groups into the benzotriazole derivatives via lithiation with subsequent displacement of the benzotriazole group would afford methine derivatives with three different substituents.

3.2 Results and Discussion

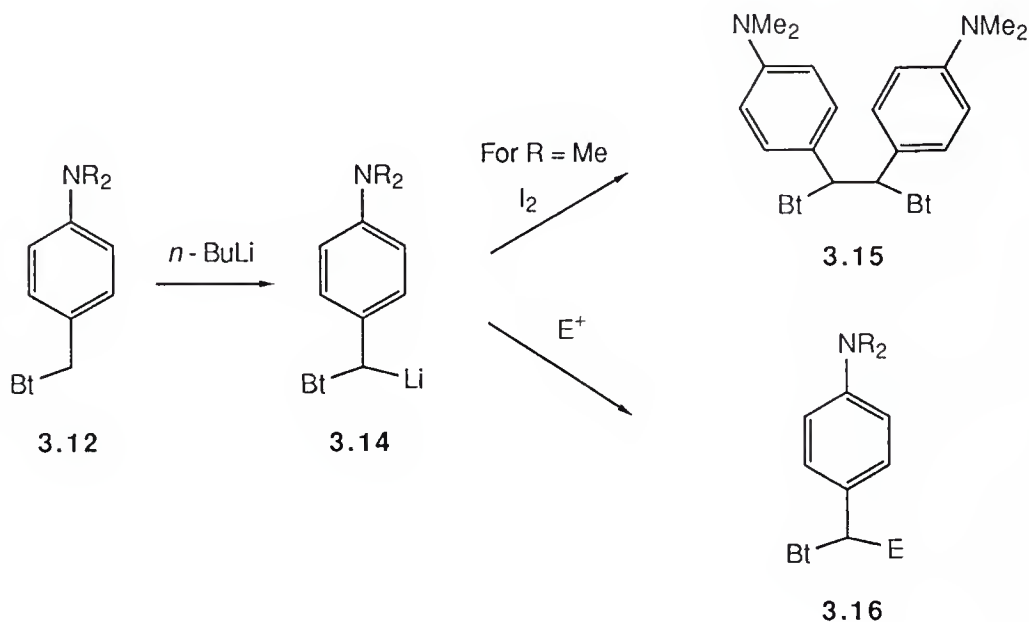
3.2.1 Lithiation of 4-(Benzotriazol-1-ylmethyl)-N,N-dialkylanilines

4-(Benzotriazol-1-ylmethyl)-N,N-dimethylaniline (3.12b) underwent lithiation smoothly with n-butyllithium

in tetrahydrofuran at $-78\text{ }^{\circ}\text{C}$ to form a deep blue colored solution. When the anion was quenched with deuterium oxide, the ^1H NMR spectrum of the isolated compound displayed the methylene proton, with a chemical shift similar to that of the starting material 3.12b, but with its integration corresponding to one proton. This indicated that the lithiation occurred exclusively at the relatively acidic benzylic methylene carbon. The chelation effect of the dimethylamino group [66JOC2047, 79JOC237] diminished due to the large acidity difference between the benzene ring proton and the methylene proton alpha to the strongly electron-withdrawing benzotriazolyl group.

The corresponding anion 3.14 also decolorized immediately on addition of one equivalent of an electrophile indicating high reactivity of the anion. Reaction of the anion 3.14 with electrophiles such as methyl iodide, benzyl bromide, aldehydes and ketones afforded the desired products 3.16 in high yields (Scheme 3.3, Table 3.1). With aldehydes, generally two diastereomeric isomers were obtained. In particular, when *p*-tolualdehyde was used, the diastereomers, obtained in a ratio of 2.5:1, were isolated by repeated recrystallization of the crude product from methanol, followed by column chromatography. With pyridine-4-carboxaldehyde, the two isomers, obtained in equal amounts, were similarly isolated. With esters as

electrophiles, the yields were low, possibly due to further attacks of the lithio salt 3.14 on the products yielding enolate anions. The reaction mixtures in these cases turned dark upon warming to room temperature. Work-up at $-78\text{ }^{\circ}\text{C}$ did not alter the outcome. With ethyl isonicotinate, a complex mixture was obtained which was not characterized. Treatment of the anion 3.14 with iodine gave 1,2-bis(4-N,N-dimethylaminophenyl)-1,2-bis(benzotriazol-1-yl)ethane (3.15). Reactions of the lithio derivative of 4-(benzotriazol-1-ylmethyl)-N,N-diethyl-aniline 3.12c with methyl iodide and cyclohexanone afforded the corresponding products 3.16i-j indicating again that lithiation occurred completely at the relatively acidic benzylic methylene carbon.



Scheme 3.3

Table 3.1 Lithiation of 4-(Benzotriazol-1-ylmethyl)-N,N-dialkylanilines

Substrate	Electrophile	Products	E	Yield ^a (%)	M.p. (°C)
3.12b	I ₂	3.15	-	30	210 (dec.)
3.12b	D ₂ O	3.16a	D	90	165-166
3.12b	CH ₃ I	3.16b	CH ₃	99	107-109
3.12b	PhCH ₂ Br	3.16c	PhCH ₂	68	147-149
3.12b	p-CH ₃ C ₆ H ₄ CHO	3.16d	p-CH ₃ C ₆ H ₄ CH(OH)	50 ^b (79 ^c)	199-201
3.12b	p-CH ₃ C ₆ H ₄ CHO	3.16d	p-CH ₃ C ₆ H ₄ CH(OH)	17 ^d (79 ^c)	187-189
3.12b	Ph ₂ C=O	3.16e	Ph ₂ C(OH)	85	202-204
3.12b	(CH ₂) ₅ C=O	3.16f	(CH ₂) ₅ C(OH)	77	205-207
3.12b	p-CH ₃ C ₆ H ₄ CO ₂ Et	3.16g	p-CH ₃ C ₆ H ₄ C(=O)	62	159-161
3.12b	Pyridine-4-CHO	3.16h	Pyridine-4-CH(OH)	18 ^b (65 ^c)	218-219
3.12b	Pyridine-4-CHO	3.16h	Pyridine-4-CH(OH)	10 ^d (65 ^c)	190-192
3.12c	CH ₃ I	3.16i	CH ₃	72	79-81
3.12c	(CH ₂) ₅ C=O	3.16j	(CH ₂) ₅ C(OH)	69	181-183

^a Isolated yields.^b Isomer I.^c Total yield of both isomers.^d Isomer II.

The structures of the products 3.15 and 3.16 were confirmed by their NMR spectra and elemental analyses. The methine carbons were observed at 58.7–70.4 ppm (the corresponding carbon for 3.16a was observed as a triplet centered at 51.8 ppm). The methine protons usually resonated between 5.50–5.98 ppm except for compounds 3.16g and 3.15. The carbonyl group shifted the methine proton in 3.16g downfield to 7.78 ppm. The corresponding methine proton in 3.15 was observed as a singlet at 7.67 ppm as evidenced by 2-D NMR spectra (COSY and HETCOR).

Table 3.2 ^1H and ^{13}C NMR Chemical Shifts (δ) for the Methine Groups in 3.15 and 3.16

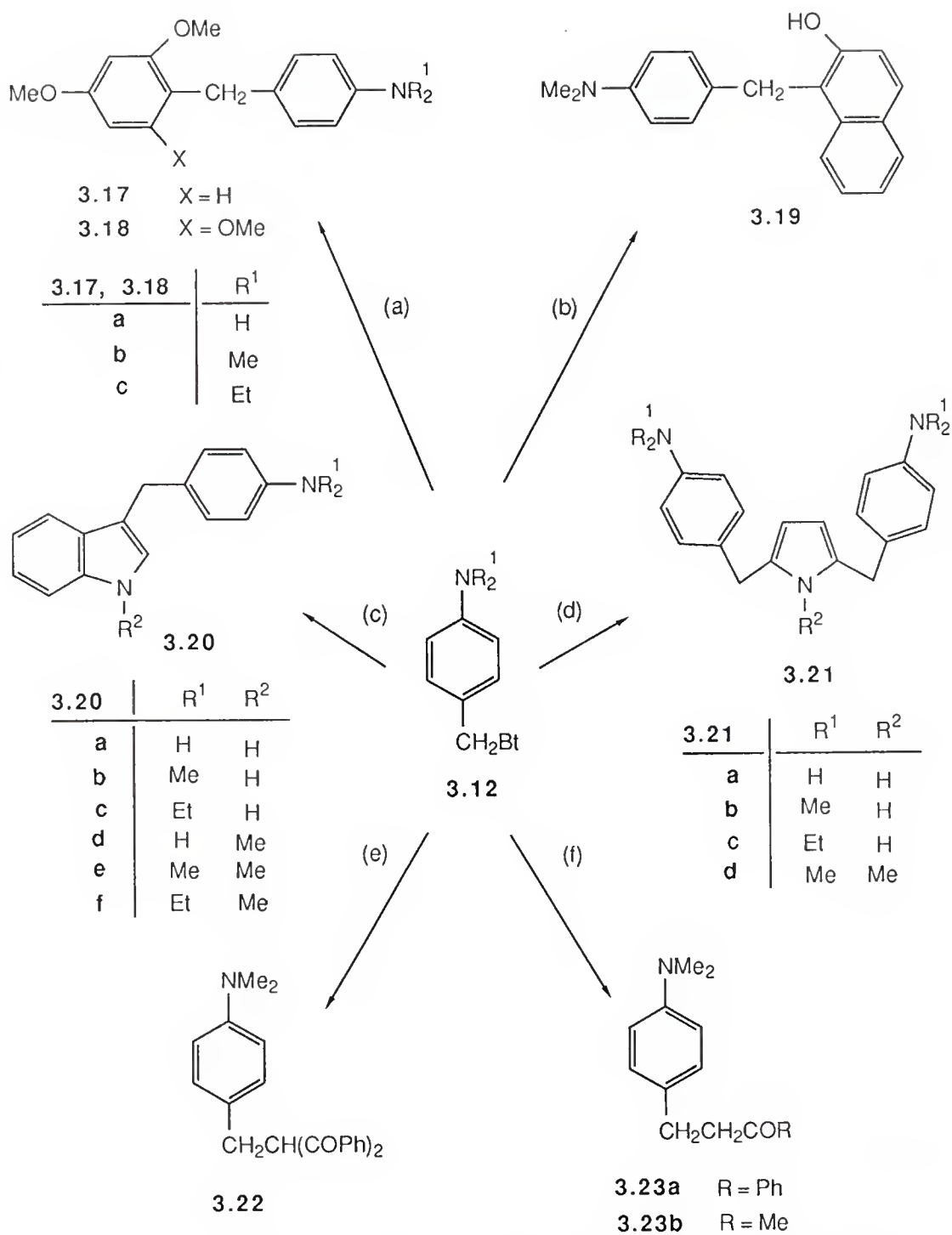
Compound	Substituent	$\delta_{\text{H}}(\text{R}_3\text{CH})$	$\delta_{\text{C}}(\text{R}_3\text{CH})$
3.15 ^a	–	7.67	63.3
3.16a	D	5.70	51.8
3.16b	Me	5.98	58.7
3.16c	PhCH ₂	5.90	64.9
3.16d	p-CH ₃ C ₆ H ₄ CH(OH)	5.72	70.0
3.16d	p-CH ₃ C ₆ H ₄ CH(OH)	5.65	68.8
3.16e	Ph ₂ C(OH)	5.83	68.2
3.16f	(CH ₂) ₅ C(OH)	5.50	70.4
3.16g	p-CH ₃ C ₆ H ₄ C(=O)	7.78	68.3
3.16h	Pyridine-4-CH(OH)	5.61	69.8
3.16h	Pyridine-4-CH(OH)	5.63	68.3
3.16i	Me	5.96	58.7
3.16j	(CH ₂) ₅ C(OH)	5.50	70.4

^a For structure of compound 3.15, see Scheme 3.3.

3.2.2 Displacement of the Benzotriazolyl Moiety by Electron-rich Aromatic Compounds

The benzotriazolyl moiety in compounds 3.12a-c has been displaced efficiently by a series of aromatic systems, including 1,3-dimethoxybenzene, 1,3,5-trimethoxybenzene, indoles, pyrroles, and 2-naphthol under reaction conditions similar to those for the synthesis of bisanilines (see section 2.4.3 in Chapter II). Thus, heating a mixture of 3.12 and the appropriate aromatic compound, in a 50% aqueous methanolic solution in the presence of concentrated hydrochloric acid, gave the desired products 3.17-3.21 in good to excellent yields (See Scheme 3.4 and Table 3.3). Except for 3.19 and 3.20b, all these compounds are novel. Thus this method provides an effective synthesis of compounds containing two aromatic rings connected via a methylene bridge.

The 4-(N,N-dimethylanilino) analogs, 3.19 and 3.20b, have been frequently reported in the literature. The 2-naphthol derivative 3.19 can be directly prepared by the reaction of 2-naphthol, paraformaldehyde and N,N-dimethylaniline in the presence of piperidine [45USP2375168]. With aqueous formaldehyde and acetic acid in the presence of a catalytic amounts of N-methylaniline, 3.19 was obtained in 90% yield (Scheme 3.5). The indole derivative 3.20b has been prepared by initial treatment of the salt 3.24 with phenylhydrazine to afford 3.25, which by treatment with



Scheme 3.4

Table 3.3 Reaction of 4-(Benzotriazol-1-ylmethyl)anilines with Nucleophiles.

Entry	Reaction time (h)	Yield ^a (%)	M.p. (°C)	Purification solvent
3.17a	3 d ^b	53	oil	1:2 ^c
3.17b	3 d	50	oil	2:1 ^c
3.17c	4 d	68	oil	pet. ether ^c
3.18a	57	80	123-124	1:1 ^c
3.18b	27	73	89-90	8:1 ^c
3.18c	3 d	72	96-97	hexane ^d
3.19	7 d	64	141-143 ^e	aq. ethanol ^d
3.20a	2 d	92	130-132	-f
3.20b	7	96	143-145 ^g	-f
3.20c	3 d	95	134-136	-f
3.20d	3 d	85	75-76	2:1 ^c
3.20e	20	98	oil	-f
3.20f	44	82	oil	18:1 ^c
3.21a	55	29	oil	2:1 ^c
3.21b	21	52	oil	2:1 ^c
3.21c	5 d	41	72-74	40:1 ^c
3.21d	24	45	130-132	40:1 ^c
3.22	27	25	131-133 ^h	15:1 ⁱ
3.23a	6 d	48	oil ^j	40:1 ^c
3.23b	6 d	36	44-46 ^k	12:1 ^c

^a Isolated yields.

^b d = days.

^c Column chromatography on alumina basic. The ratio indicates petroleum ether (38-56 °C) to EtOAc, v/v. Further purification for the analytically pure sample is described for the particular compound in the Experimental section.

^d Recrystallization solvent.

^e Lit. [34JCS1136] m.p. 143 °C.

^f After cooling the reaction mixture, the precipitate was collected as the essentially pure product.

^g Lit. [67JOC3101] m.p. 141-144 °C.

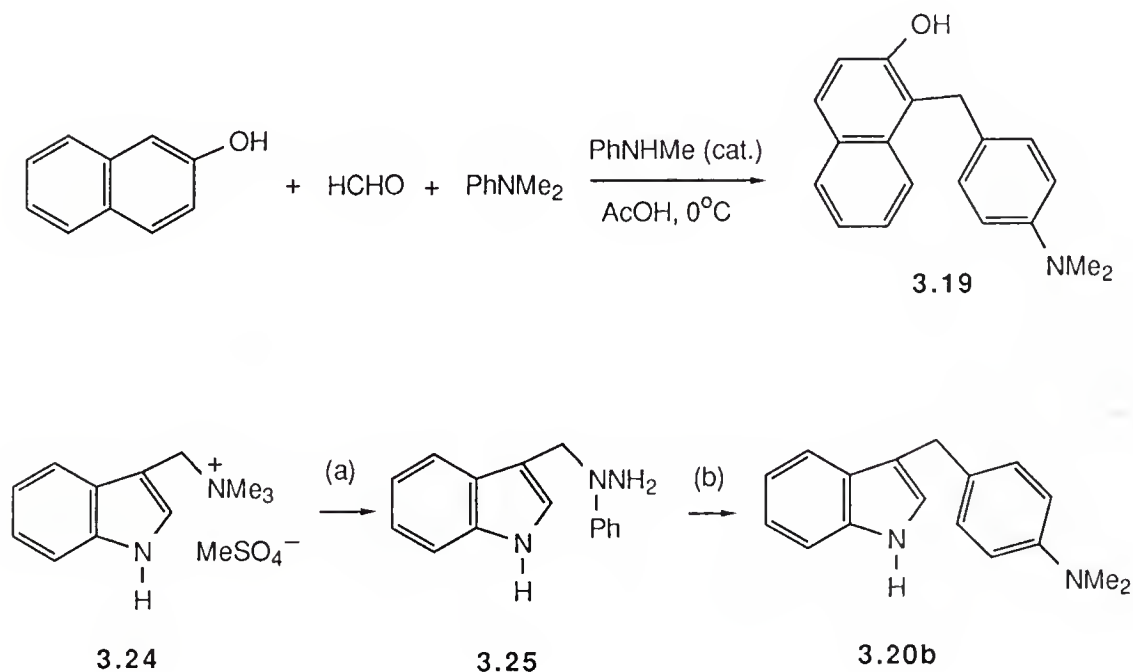
^h Lit. [34JCS1136] m.p. 132-133 °C.

ⁱ Column chromatography on silica gel, the ratio indicates petroleum ether (38-56 °C) to EtOAc, v/v.

^j Lit. [56JA4950] m.p. 51 °C.

^k Lit. [63JMC153] m.p. 47-48 °C.

N,N-dimethylaniline afforded 3.20b in 96% yield [56CB1195]. These literature yields are comparable with those obtained by our method, and some of the other methylene compounds discussed in this Chapter could probably also be made by the literature methods. However, those methods are strictly restricted to compounds with -CH₂- linkages and no previous examples are known for a -CHX- linkage. Thus, the preparation of such -CHX- derivatives by our method, as will be described later, makes it uniquely valuable.



(a) PhNHNH₂, NaOH, H₂O
 (b) i) PhNMe₂, EtOH/THF (1:1); ii) 5 N HCl; iii) 2 N NaOH

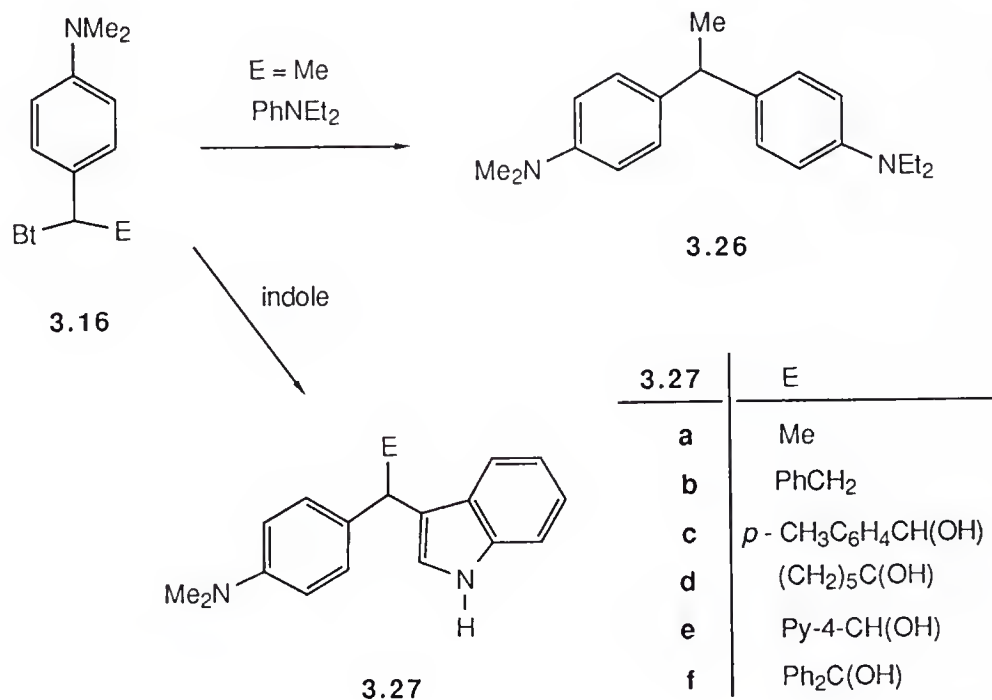
Scheme 3.5

Regiospecificity in the displacement reactions is controlled both by the electron densities at different positions and by steric hindrance. Electrophilic substitution at the C-3(β) position is characteristic of the indole ring [79MI1, 85JOC5451]. Consequently, reaction of 3.12 with indoles gave derivatives 3.20. Pyrrole reacts with electrophiles exclusively at the α -positions [81TL4901, 84MI1, 85S353, 88H1855]. In our case, both the 2- and the 5-positions of pyrrole reacted to afford the products 3.21. 1,3-Dimethoxybenzene reacts at the 4-position since the 2-position is more sterically hindered. For 1,3,5-trimethoxybenzene, there is only one kind of reactive site. 2-Naphthol has its highest electron density at the 1-position, thus the 1-substituted product 3.19 was obtained.

The reaction of 3.12b with other nucleophiles was also tested and it was shown to be reactive towards 1,3-dicarbonyl compounds. The product obtained was dependent on the conditions employed. Thus, heating a mixture of 3.12b with the appropriate 1,3-dicarbonyl compound in 50% aqueous methanol containing concentrated hydrochloric acid under reflux for several days, afforded compounds of type 3.23, where one of the carbonyl groups had been displaced. The properties of the compounds thus obtained have been compared with those reported in the literature and their structures were further confirmed by

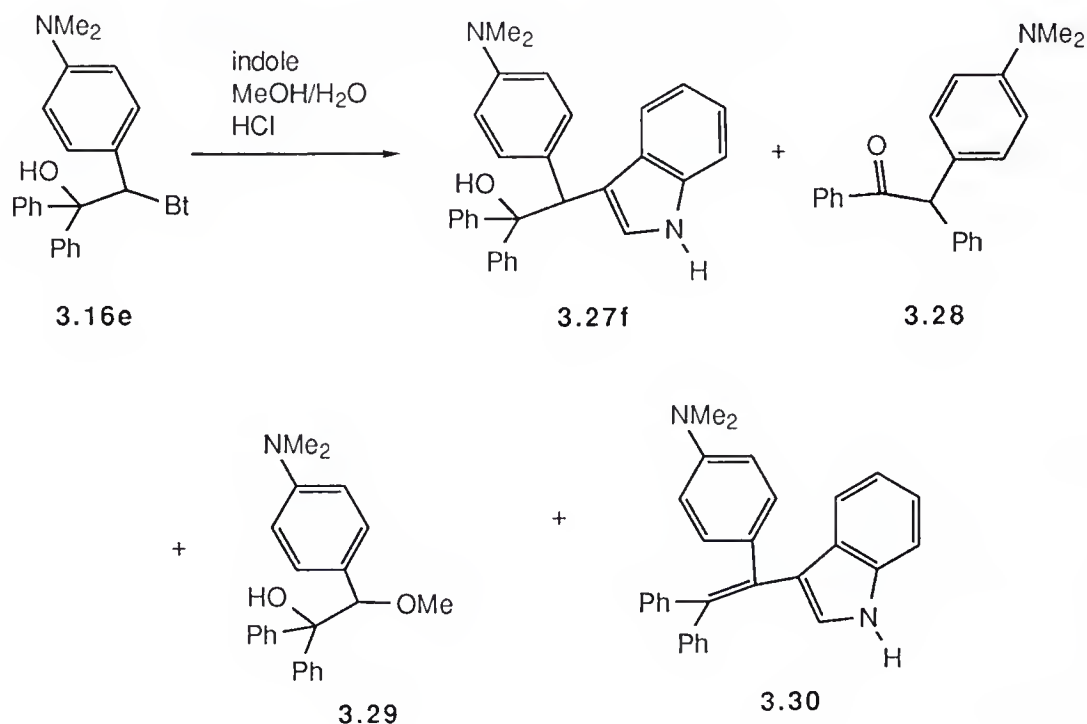
their NMR spectra. When the reaction was carried out in an aprotic solvent such as toluene using a Lewis acid catalyst (zinc bromide), the product 3.22 was obtained in 25% yield by direct displacement of the benzotriazole.

The displacement of benzotriazole from the lithiated derivatives 3.16 was also effected by various nucleophiles. Reaction of 3.16a with *N,N*-diethylaniline afforded the desired product 3.26. The displacement of the benzotriazolyl moiety was also accomplished by indole, as evidenced by the production of compounds 3.27a-f in moderate to high yields (Scheme 3.6 and Table 3.4).



Scheme 3.6

In the instances where the electrophile contained a phenyl ring, low yields were obtained. With the benzophenone derivative (3.16e), the formation of 3.27f in 26% yield was accompanied by the formation of other compounds of which three were isolated and characterized. These arose from (i) the migration of the phenyl group to give the ketone 3.28, (ii) the direct displacement of the benzotriazolyl by methoxy group (from methanol) giving 3.29, and (iii) the dehydration of 3.27f to produce 3.30 (Scheme 3.7). This strengthens our belief that in such reactions, the initial ionization generated the benzotriazolyl anion and the relatively stable benzylic cation which was then trapped by the various nucleophiles.



Scheme 3.7

Table 3.4 Reactions of Substituted Products 3.16 with N,N-Dialkylaniline and Indole

Substrate	Compound	Reaction time (h)	Yield ^a (%)	M.p. (°C)
3.16b	3.26	4 ^b	67	oil
3.16b	3.27a	18	91 ^c	152-154
3.16c	3.27b	40	82 ^c	119-121
3.16d	3.27c	72	38 ^d	170-172
3.16f	3.27d	18	86 ^c	162-164
3.16h	3.27e	20	70 ^c	183-185
3.16e	3.27f	18	26 ^e	211-213
3.16e	3.28	18	5 ^e	127-129
3.16e	3.29	18	9 ^e	184-186
3.16e	3.30	18	10 ^e	209-211

^a Isolated yields.

^b HOAc was used as the solvent.

^c After cooling the reaction mixture, the precipitate was collected as the essentially pure product.

^d Chromatography on silica gel from petroleum ether (38-56 °C)/EtOAc, 2:1, v/v.

^e Chromatography on silica gel from petroleum ether (38-56 °C)/EtOAc, 12:1, v/v, followed by recrystallization from hexane/EtOAc.

The structures of the derivatives 3.17-3.21, 3.26-3.27 were confirmed by their spectral data and elemental analyses. The methylene protons appeared in the region of 3.73-4.33 ppm (and between 3.96-5.43 ppm for the methine protons). The corresponding methylene carbon resonated in

the region of 27.0–34.1 ppm (35.8–51.3 ppm for the methine carbon). The upfield shift of the methylene and the methine signals, compared to those of the corresponding benzotriazolyl adducts, indicated the loss of the electron-withdrawing benzotriazolyl moiety.

Table 3.5 ^1H and ^{13}C NMR Chemical Shifts (δ) for the Methylene or Methine Groups in 3.17–3.21, 3.26–3.27

Comp.	$\delta_{\text{H}}(\underline{\text{CH}}_2)$	$\delta_{\text{C}}(\underline{\text{CH}}_2)$	Comp.	$\delta_{\text{H}}(\underline{\text{CH}}_2)$ or ($\underline{\text{CH}}$)	$\delta_{\text{C}}(\underline{\text{CH}}_2)$ or ($\underline{\text{CH}}$)
3.17a	3.77	34.1	3.21a	3.73	33.1
3.17b	3.80	34.0	3.21b	3.73	32.9
3.17c	3.78	33.9	3.21c	3.77	33.0
3.18a	3.81	27.2	3.21d	3.80	32.3
3.18b	3.83	27.0			
3.18c	3.81	27.0			
3.19	4.33	29.7	3.26	3.96	42.7
3.20a	3.99	30.7	3.27a	4.28	35.8
3.20b	4.01	30.5	3.27b	4.39	43.7
3.20c	3.98	30.3	3.27c	4.49	50.7
3.20d	3.95	30.5	3.27d	4.21	51.3
3.20e	3.97	30.3	3.27e	4.47	50.5
3.20f	3.97	30.3	3.27f	5.43	50.6

3.3 Conclusions

4-(Benzotriazol-1-ylmethyl)-N,N-dialkylanilines undergo smooth lithiation at the methylene carbon and give derivatives upon treatment of the anion with a variety of electrophiles. Displacement of the benzotriazolyl moiety in compounds 3.12 and their substituted products 3.16 lead to a series of novel unsymmetrical methanes containing two or three fragments. These compounds, containing an aniline fragment, if oxidized, could find potential applications as dyestuffs due to the extended conjugation.

3.4 Experimental

The apparatus and general procedures applied in this Chapter are identical to those described in Chapter II with the following additions.

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Electrophiles were purified by standard methods before use. Lithiation reactions were performed in oven-dried glassware under a nitrogen atmosphere. Column chromatography was carried out using alumina basic (Brockman Activity I, 80-200 mesh) or MBS silica gel (230-400 mesh) as indicated. Exact mass measurements were performed on a KRATOS/AE1-MS 30 mass spectrometer.

Compounds 3.12a-c were prepared according to the procedure described in Chapter II.

3.4.1 General Procedure for the Preparation of Substituted 4-(Benzotriazol-1-ylmethyl)anilines

To a solution of the substrate (2.5 mmol) in THF (80 ml) at -78 °C was added dropwise *n*-BuLi (2.5 M in hexane; 1.0 ml, 2.5 mmol). The mixture was stirred at -78 °C for 2 h and then a solution of the appropriate electrophile (2.5 mmol) in THF (5 ml) was added slowly. The mixture was kept at -78 °C for a few hours and allowed to warm to room temperature overnight. Water (30 ml) was added to quench the reaction, and the solution was extracted with diethyl ether (3 × 50 ml). The combined ether extracts were washed with water (50 ml) and dried over MgSO₄. The solvent was removed and the residue purified as described for each individual compound.

This general procedure applies to the preparation of 3.16a-j. Physical data of the products, substrates and electrophiles used, and yields are given in Table 3.1.

1,2-Bis(4-N,N-dimethylaminophenyl)-1,2-bis(benzotriazol-1-yl)ethane (3.15). To a solution of 4-(benzotriazol-1-ylmethyl)-N,N-dimethylaniline (1.26 g, 5 mmol) in THF (160 ml) at -78 °C was added *n*-BuLi (2.5 M in hexane; 2.0 ml, 5 mmol) via a syringe under nitrogen. The

mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and then a solution of iodine (1.4 g, 5.5 mmol) in THF (10 ml) was added. The whole was stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h and water (30 ml) was added at $-78\text{ }^{\circ}\text{C}$. The resultant mixture was allowed to warm to room temperature overnight and extracted with methylene chloride ($3 \times 80\text{ ml}$). The organic layer was washed with saturated sodium thiosulfate solution (150 ml) and dried (MgSO_4). The solvent was evaporated and the black residue chromatographed on alumina basic from petroleum ether ($38\text{--}56\text{ }^{\circ}\text{C}$)/EtOAc, 6:1, v/v, to give 3.15 (0.38 g, 30%) as microcrystals. ^1H NMR δ 2.77 (s, 12 H), 6.56 (d, $J = 8.8\text{ Hz}$, 4 H), 7.28 (t, $J = 8.0\text{ Hz}$, 2 H), 7.53 (t, $J = 8.0\text{ Hz}$, 2 H), 7.67 (s, 2 H), 7.72 (d, $J = 8.8\text{ Hz}$, 4 H), 7.80 (d, $J = 8.0\text{ Hz}$, 2 H), 8.34 (d, $J = 8.0\text{ Hz}$, 2 H); ^{13}C NMR δ 39.7, 63.3, 111.1, 111.7, 118.7, 123.2, 124.0, 127.1, 129.3, 132.5, 144.5, 149.9.

Anal. Calcd for $\text{C}_{30}\text{H}_{30}\text{N}_8$: C, 71.69; H, 6.02; N, 22.29. Found: C, 71.50; H, 6.02; N, 22.54.

(Benzotriazol-1-yl)-(4-N,N-dimethylaminophenyl)-deuteriomethane (3.16a). Obtained as needles

(recrystallized from methanol). ^1H NMR δ 2.89 (s, 6 H), 5.70 (s, 1 H), 6.62–6.65 (m, 2 H), 7.18–7.37 (m, 5 H), 8.00–8.03 (m, 1 H); ^{13}C NMR δ 40.3, 51.8 (t, $J = 21\text{ Hz}$), 110.0, 112.3, 119.8, 121.8, 123.6, 127.0, 128.8, 132.6, 146.3, 150.4. MS (HR) for $\text{C}_{15}\text{H}_{15}\text{DN}_4$ Calcd: 253.1437. Found: 253.1423.

4-[1-(Benzotriazol-1-yl)ethyl]-N,N-dimethylaniline
(3.16b). Obtained as prisms (recrystallized from methanol). ^1H NMR δ 2.10 (d, $J = 7$ Hz, 3 H), 2.89 (s, 6 H), 5.98 (q, $J = 7$ Hz, 1 H), 6.63 (d, $J = 8.8$ Hz, 2 H), 7.17 (d, $J = 8.8$ Hz, 2 H), 7.24-7.30 (m, 3 H), 8.00-8.04 (m, 1 H); ^{13}C NMR δ 20.9, 40.3, 58.7, 110.4, 112.2, 119.7, 123.5, 126.6, 127.20, 127.24, 132.2, 146.3, 150.1.

Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 72.32; H, 6.92; N, 21.28.

4-[(1-Benzotriazol-1-yl)-(1-benzyl)]methyl-N,N-dimethylaniline (3.16c). Obtained as plates (recrystallized from methanol/EtOAc). ^1H NMR δ 2.88 (s, 6 H), 3.70 (dd, $J = 6.6, 14.0$, Hz, 1 H), 4.07 (dd, $J = 8.8, 14.0$ Hz, 1 H), 5.90 (dd, $J = 6.6, 8.8$ Hz, 1 H), 6.61 (d, $J = 8.8$ Hz, 2 H), 7.03-7.30 (m, 10 H), 7.95-7.99 (m, 1 H); ^{13}C NMR δ 40.3, 41.2, 64.9, 109.8, 112.2, 119.7, 123.5, 126.1, 126.5, 126.8, 127.8, 128.3, 129.0, 132.7, 137.5, 146.0, 150.2.

Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_4$: C, 77.16; H, 6.48; N, 16.36. Found: C, 77.15; H, 6.52; N, 16.64.

1-(4-Tolyl)-2-(benzotriazol-1-yl)-2-(4-dimethylamino-phenyl)ethanol (3.16d). Recrystallization of the crude product from methanol gave the pure isomer I (50%) as needles. The residue after evaporation of the solvent was

chromatographed on alumina basic from petroleum ether (38-56 °C)/EtOAc, 4:1, v/v, to give the pure isomer II (17%) as microcrystals and a mixture of both isomers (12%). The total yield was 79%.

Isomer I. ^1H NMR δ 2.26 (s, 3 H), 2.80 (s, 6 H), 4.12 (d, J = 4.0 Hz, 1 H), 5.72 (d, J = 8.8 Hz, 1 H), 5.89 (dd, J = 4.0, 8.8 Hz, 1 H), 6.44 (d, J = 8.8 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 7.01 (d, J = 8.0 Hz, 2 H), 7.12 (d, J = 8.0 Hz, 2 H), 7.21-7.35 (m, 3 H), 7.96 (d, J = 8.0, 1 H); ^{13}C NMR δ 21.1, 40.1, 70.0, 76.0, 110.2, 111.9, 119.5, 123.3, 123.9, 126.9, 127.2, 128.4, 128.8, 133.5, 136.7, 137.3, 145.6, 150.0.

Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}$: C, 74.17; H, 6.49; N, 15.04. Found: C, 73.86; H, 6.57; N, 15.12.

Isomer II. ^1H NMR δ 2.22 (s, 3 H), 2.88 (s, 6 H), 3.60 (s, br, 1 H), 5.65 (d, J = 6.0 Hz, 1 H), 5.93 (d, J = 6.0 Hz, 1 H), 6.57-6.60 (m, 2 H), 6.96-6.98 (m, 2 H), 7.12-7.26 (m, 7 H), 7.92-7.96 (m, 1 H); ^{13}C NMR δ 21.0, 40.2, 68.8, 75.0, 109.7, 111.9, 119.6, 122.0, 123.8, 126.5, 127.1, 128.7, 129.4, 132.9, 136.8, 137.4, 145.2, 150.4.

Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}$: C, 74.17; H, 6.49; N, 15.04. Found: C, 74.06; H, 6.69; N, 14.80.

2-(Benzotriazol-1-yl)-2-(4-dimethylaminophenyl)-1,1-diphenylethanol (3.16e). Obtained as plates (recrystallized from methanol). ^1H NMR δ 1.65 (s, 1 H), 2.81 (s, 6 H), 5.83 (s, 1 H), 6.39-6.41 (m, 2 H), 6.55 (s, 1 H), 6.84-6.87 (m, 2 H), 7.00-7.55 (m, 12 H), 7.96 (d, $J = 8.0$ Hz, 1 H); ^{13}C NMR δ 40.2, 68.2, 81.4, 109.5, 111.3, 120.0, 122.1, 124.2, 125.5, 126.5, 126.8, 126.9, 127.7, 127.8, 128.2, 129.7, 133.2, 143.3, 144.8, 145.7, 149.9.

Anal. Calcd for $\text{C}_{28}\text{H}_{26}\text{N}_4\text{O}$: C, 77.39; H, 6.03; N, 12.89. Found: C, 77.01; H, 6.06; N, 12.97.

1-[(Benzotriazol-1-yl)(4-dimethylaminophenyl)]methylcyclohexan-1-ol (3.16f). Obtained as needles (recrystallized from methanol). ^1H NMR δ 1.20-1.66 (m, 10 H), 2.88 (s, 6 H), 4.01 (s, 1 H), 5.50 (s, 1 H), 6.62 (d, $J = 8.8$ Hz, 2 H), 7.26-7.53 (m, 5 H), 8.03 (d, $J = 8.0$ Hz, 1 H); ^{13}C NMR δ 21.5, 21.8, 25.5, 35.0, 36.1, 40.2, 70.4, 74.3, 109.8, 111.8, 119.8, 122.8, 124.1, 127.5, 129.8, 133.8, 144.9, 150.3.

Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}$: C, 71.97; H, 7.48; N, 15.99. Found: C, 71.89; H, 7.51; N, 16.37.

2-(Benzotriazol-1-yl)-2-(4-dimethylaminophenyl)-4'-methylacetophenone (3.16g). Obtained as plates (trituated with diethyl ether). ^1H NMR δ 2.32 (s, 3 H), 2.87 (s, 6 H), 6.61 (d, $J = 8.8$ Hz, 2 H), 7.17-7.30 (m, 7 H), 7.78

(s, 1 H), 7.91–8.00 (m, 3 H); ^{13}C NMR δ 21.5, 39.8, 68.3, 111.8, 112.1, 119.1, 119.5, 123.4, 127.0, 129.0, 129.4, 130.2, 131.9, 133.3, 144.8, 146.4, 150.5, 192.7.

Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}$: C, 74.57; H, 5.99; N, 15.12. Found: C, 74.60; H, 6.17; N, 15.14.

2-(Benzotriazol-1-yl)-2-(4-dimethylaminophenyl)-1-(pyrid-4-yl)ethanol (3.16h). Recrystallization of the crude product from methanol gave the pure isomer I (18%) as microcrystals. The residue after evaporation of the solvent was recrystallized again from methanol to give the pure isomer II (10%) as plates. The residue consisted of a mixture of both isomers (37%). The total yield was 65%.

Isomer I. ^1H NMR δ 2.00 (s, br, 1 H), 2.87 (s, 6 H), 5.61 (d, $J = 8.0$ Hz, 1 H), 5.93 (d, $J = 8.8$ Hz, 1 H), 6.48 (d, $J = 8.0$ Hz, 2 H), 6.90 (d, $J = 8.0$ Hz, 2 H), 7.11 (d, $J = 5.0$ Hz, 2 H), 7.3–7.4 (m, 3 H), 8.00 (d, $J = 8.0$ Hz, 1 H), 8.41 (d, $J = 5.0$ Hz, 2 H); ^{13}C NMR δ 40.1, 69.8, 75.2, 110.1, 112.0, 119.8, 122.1, 122.2, 124.3, 127.6, 128.4, 133.4, 145.7, 148.8, 149.4, 150.4.

Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_5\text{O}$: C, 70.18; H, 5.89; N, 19.48. Found: C, 69.94; H, 5.94; N, 19.54.

Isomer II. ^1H NMR δ 2.88 (s, 6 H), 4.90 (s, br, 1 H), 5.63 (d, $J = 6.0$ Hz, 1 H), 5.98 (d, $J = 6.0$ Hz, 1 H), 6.55

(d, $J = 8.8$ Hz, 2 H), 7.1–7.3 (m, 7 H), 7.96 (d, $J = 7.0$ Hz, 1 H), 8.30 (d, $J = 3.0$ Hz, 2 H); ^{13}C NMR δ 40.1, 68.3, 73.8, 109.7, 110.8, 119.7, 121.1, 121.7, 124.1, 127.4, 129.4, 132.9, 145.3, 149.2, 149.4, 150.5.

Anal. Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_5\text{O}$: C, 70.18; H, 5.89; N, 19.48. Found: C, 70.30; H, 5.91; N, 19.72.

4-(1-Benzotriazol-1-yl)ethyl-N,N-diethylaniline (3.16i). Obtained as plates (column chromatography on silica gel from petroleum ether (38–56 °C)/EtOAc, 9:1, v/v). ^1H NMR δ 1.10 (t, $J = 7.0$ Hz, 6 H), 2.10 (d, $J = 7.0$ Hz, 3 H), 3.28 (q, $J = 7.0$ Hz, 4 H), 5.96 (q, $J = 7.0$ Hz, 1 H), 6.57 (d, $J = 8.8$ Hz, 2 H), 7.15 (d, $J = 8.8$ Hz, 2 H), 7.23–7.30 (m, 3 H), 8.00 (d, $J = 8.0$ Hz, 1 H); ^{13}C NMR δ 12.4, 20.9, 44.1, 58.7, 110.5, 111.5, 119.6, 123.4, 126.1, 126.5, 127.5, 132.2, 146.3, 147.5.

Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_4$: C, 73.44; H, 7.53; N, 19.03. Found: C, 73.16; H, 7.67; N, 19.08.

1-[(Benzotriazol-1-yl)(4-N,N-diethylaminophenyl)]-methyl cyclohexan-1-ol (3.16j). Obtained as microcrystals (recrystallized from methanol). ^1H NMR δ 1.08 (t, $J = 7.0$ Hz, 6 H), 1.2–1.8 (m, 10 H), 3.26 (q, $J = 7.0$ Hz, 4 H), 4.02 (s, 1 H), 5.50 (s, 1 H), 6.55 (d, $J = 8.0$ Hz, 2 H), 7.3–7.6 (m, 5 H), 8.03 (d, $J = 8.0$ Hz, 1 H); ^{13}C NMR δ 12.4, 21.5, 21.7, 25.5, 34.9, 36.0, 44.0, 70.4, 74.3,

109.8, 110.8, 119.7, 121.4, 124.0, 127.3, 130.0, 133.7, 144.8, 147.5.

Anal. Calcd for $C_{23}H_{30}N_4O$: C, 72.98; H, 7.99; N, 14.80. Found: C, 72.71; H, 8.14; N, 14.96.

3.4.2 General Procedure for the Displacement of the Benzotriazolyl Moiety by Nucleophiles

To a stirred solution of the substrate (5 mmol) in MeOH (30 ml) under reflux was added a solution of the appropriate nucleophile (5 mmol) and dilute hydrochloric acid (3%; 30 ml). The resulting mixture was heated under reflux for the appropriate time followed by addition of an aqueous KOH solution (1 M; 50 ml) and subsequently cooled. The products were isolated by filtration for 3.20a-c, 3.20e, 3.27a-b, and 3.27d-e. For other products, the reaction mixture was extracted with diethyl ether (3 × 40 ml) and dried ($MgSO_4$). The solvent was evaporated and the residue was purified.

This general procedure applies to the displacement products except 3.22. Physical data of all the products, yields, reaction time, and methods of purification are given in Tables 3.3 and 3.4. Further purification for the analytically pure sample is described for the particular compound.

2-(4-Aminophenylmethyl)-1,5-dimethoxybenzene (3.17a).

Obtained as an oil. ^1H NMR δ 3.42 (s, br, 2 H), 3.73 (s,

br, 6 H), 3.77 (s, 2 H), 6.3-6.4 (m, 2 H), 6.5-6.6 (m, 2 H), 6.90-6.97 (m, 3 H); ^{13}C NMR δ 34.1, 55.12, 55.15, 98.3, 103.7, 115.0, 122.7, 129.5, 130.2, 131.1, 144.1, 158.0, 159.0.

Anal. Calcd for $\text{C}_{15}\text{H}_{17}\text{NO}_2$: C, 74.05; H, 7.04. Found: C, 74.33; H, 7.09.

2-(4-N,N-Dimethylaminophenylmethyl)-1,5-dimethoxybenzene (3.17b). Obtained as an oil. ^1H NMR δ 2.87 (s, 6 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 3.80 (s, 2 H), 6.3-6.7 (m, 4 H), 6.92 (d, $J = 8.0$ Hz, 1 H), 7.0-7.1 (m, 2 H); ^{13}C NMR δ 34.0, 40.8, 55.2, 55.3, 98.4, 103.8, 112.9, 122.9, 129.4, 129.5, 130.2, 148.9, 158.1, 159.1.

Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_2$: C, 75.25; H, 7.80. Found: C, 75.42; H, 7.82.

2-(4-N,N-Diethylaminophenylmethyl)-1,5-dimethoxybenzene (3.17c). Obtained as an oil. ^1H NMR δ 1.09 (t, $J = 7.0$ Hz, 6 H), 3.25 (q, $J = 7.0$ Hz, 4 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 3.78 (s, 2 H), 6.35 (dd, $J = 8.0, 2.0$ Hz, 1 H), 6.41 (d, $J = 2.0$ Hz, 1 H), 6.58 (d, $J = 8.8$ Hz, 2 H), 6.93 (d, $J = 8.0$ Hz, 1 H), 7.02 (d, $J = 8.8$ Hz, 2 H); ^{13}C NMR δ 12.5, 33.9, 44.3, 55.06, 55.11, 98.3, 103.7, 112.0, 123.0, 128.1, 129.5, 130.2, 145.9, 158.0, 159.0.

Anal. Calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_2$: C, 76.22; H, 8.42. Found: C, 76.00; H, 8.45.

2-(4-Aminophenylmethyl)-1,3,5-trimethoxybenzene

(3.18a). Obtained as needles. ^1H NMR δ 3.75 (s, 6 H), 3.77 (s, 3 H), 3.81 (s, 2 H), 6.12 (s, 2 H), 6.51-6.54 (m, 2 H), 7.01 (d, $J = 8.5$ Hz, 2 H); ^{13}C NMR δ 27.2, 55.2, 55.6, 90.5, 110.8, 115.0, 129.1, 132.3, 143.7, 158.7, 159.3.

Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.55; H, 7.11; N, 5.01.

2-(4-N,N-Dimethylaminophenylmethyl)-1,3,5-trimethoxy-

benzene (3.18b). Obtained as plates. ^1H NMR δ 2.81 (s, 6 H), 3.73 (s, 9 H), 3.83 (s, 2 H), 6.10 (s, 2 H), 6.60 (d, $J = 8.6$ Hz, 2 H), 7.10 (d, $J = 8.0$ Hz, 2 H); ^{13}C NMR δ 27.0, 40.8, 55.0, 55.4, 90.4, 110.8, 112.8, 128.8, 130.5, 148.6, 158.6, 159.3.

Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.45; H, 7.75; N, 4.63.

2-(4-N,N-Diethylaminophenylmethyl)-1,3,5-trimethoxy-

benzene (3.18c). Obtained as needles. ^1H NMR δ 1.09 (t, $J = 7.0$ Hz, 6 H), 3.26 (q, $J = 7.0$ Hz, 4 H), 3.77 (s, 6 H), 3.78 (s, 3 H), 3.81 (s, 2 H), 6.13 (s, 2 H), 6.56 (d, $J = 8.8$ Hz, 2 H), 7.08 (d, $J = 8.8$ Hz, 2 H); ^{13}C NMR δ 12.6, 27.0, 44.4, 55.3, 55.6, 90.6, 111.2, 112.1, 129.1, 129.3, 145.7, 158.7, 159.3.

Anal. Calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.82; H, 8.37; N, 4.19.

1-(4-N,N-Dimethylaminophenylmethyl)-2-naphthol

(3.19). Obtained as plates. ^1H NMR δ 2.84 (s, 6 H), 4.33 (s, 2 H), 5.40 (s, br, 1 H), 6.62-6.65 (m, 2 H), 7.06 (dd, $J = 8.7, 3.0$ Hz, 3 H), 7.29 (dt, $J = 8.0, 1.0$ Hz, 1 H), 7.42 (dt, $J = 8.0, 1.0$ Hz, 1 H), 7.64 (d, $J = 8.8$ Hz, 1 H), 7.76 (d, $J = 8.0$ Hz, 1 H), 7.94 (d, $J = 8.5$ Hz, 1 H); ^{13}C NMR δ 29.7, 40.9, 113.3, 118.0, 118.7, 123.0, 123.3, 126.5, 127.7, 128.2, 128.4, 128.8, 129.4, 133.6, 149.3, 151.4.

3-(4-Aminophenylmethyl)indole (3.20a). Obtained as microcrystals (recrystallized from aqueous methanol). ^1H NMR δ 3.51 (s, br, 2 H), 3.99 (s, 2 H), 6.57-6.61 (m, 2 H), 6.81-6.82 (m, 1 H), 7.0-7.3 (m, 5 H), 7.50 (d, $J = 8.0$ Hz, 1 H), 7.87 (s, br, 1 H); ^{13}C NMR δ 30.7, 111.0, 115.2, 116.4, 119.2, 119.3, 121.8, 122.2, 127.4, 129.4, 131.3, 136.4, 144.2.

Anal. Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.91; H, 6.39; N, 12.44.

3-(4-N,N-Dimethylaminophenylmethyl)indole (3.20b).

Obtained as needles (recrystallized from hexane). ^1H NMR δ 2.89 (s, 6 H), 4.01 (s, 2 H), 6.68 (d, $J = 8.0$ Hz, 2 H), 6.82 (s, 1 H), 7.06 (t, $J = 7.7$ Hz, 2 H), 7.14-7.30 (m, 3 H), 7.53 (d, $J = 8.0$ Hz, 1 H), 7.85 (s, br, 1 H); ^{13}C NMR δ 30.5, 40.9, 110.9, 113.0, 116.6, 119.1, 119.2, 121.8, 122.1, 127.5, 129.2, 129.4, 136.4, 149.0.

3-(4-N,N-Diethylaminophenylmethyl)indole (3.20c).

Obtained as plates (recrystallized from aqueous methanol). ^1H NMR δ 1.10 (t, $J = 7.0$ Hz, 6 H), 3.27 (q, $J = 7.0$ Hz, 4 H), 3.98 (s, 2 H), 6.60 (d, $J = 8.5$ Hz, 2 H), 6.75 (d, $J = 1.2$ Hz, 1 H), 7.0–7.2 (m, 5 H), 7.54 (d, $J = 8.0$ Hz, 1 H), 7.69 (s, br, 1 H); ^{13}C NMR δ 12.5, 30.3, 44.4, 111.0, 112.2, 116.5, 119.0, 119.1, 121.7, 122.2, 127.5, 128.2, 129.4, 136.3, 146.1.

Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.77; H, 8.05; N, 10.09.

3-(4-Aminophenylmethyl)-N-methylindole (3.20d).

Obtained as plates. ^1H NMR δ 3.40 (s, br, 2 H), 3.57 (s, 3 H), 3.95 (s, 2 H), 6.51 (dt, $J = 8.0, 2.0$ Hz, 2 H), 6.64 (s, 1 H), 7.00–7.06 (m, 3 H), 7.13–7.23 (m, 2 H), 7.49 (dt, $J = 8.0, 1.0$ Hz, 1 H); ^{13}C NMR δ 30.5, 32.3, 108.9, 114.9, 115.0, 118.5, 119.1, 121.3, 126.8, 127.7, 129.3, 131.2, 137.0, 144.2.

Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.66; H, 6.95; N, 11.87.

3-(4-N,N-Dimethylaminophenylmethyl)-N-methylindole (3.20e). Obtained as an oil. ^1H NMR δ 2.81 (s, 6 H), 3.52 (s, 3 H), 3.95 (s, 2 H), 6.60–6.66 (m, 3 H), 7.0–7.2 (m, 5 H), 7.51 (dt, $J = 8.0, 1.0$ Hz, 1 H); ^{13}C NMR δ 30.3, 32.3, 40.7, 108.9, 112.8, 115.0, 118.5, 119.1, 121.3, 126.8,

127.8, 129.1, 129.4, 137.0, 148.9.

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 82.01; H, 7.92; N, 10.63.

3-(4-N,N-Diethylaminophenylmethyl)-N-methylindole (3.20f). Obtained as an oil. ^1H NMR δ 1.09 (t, $J = 7.0$ Hz, 6 H), 3.25 (q, $J = 7.0$ Hz, 4 H), 3.57 (s, 3 H), 3.97 (s, 2 H), 6.59 (dt, $J = 8.7, 2.0$ Hz, 2 H), 6.85 (s, 1 H), 7.01-7.23 (m, 5 H), 7.54 (dt, $J = 8.0, 1.0$ Hz, 1 H); ^{13}C NMR δ 12.5, 30.3, 32.3, 44.3, 108.9, 112.1, 115.2, 118.5, 119.2, 121.3, 126.8, 127.9, 128.2, 129.3, 137.0, 146.0.

Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58. Found: C, 82.03; H, 8.39; N, 9.47.

2,5-Bis(4-aminophenylmethyl)pyrrole (3.21a). Obtained as an oil. ^1H NMR δ 3.46 (s, br, 4 H), 3.73 (s, 4 H), 5.78 (d, $J = 2.6$ Hz, 2 H), 6.53-6.56 (m, 4 H), 6.90-6.94 (m, 4 H), 7.58 (s, br, 1 H); ^{13}C NMR δ 33.1, 105.9, 115.2, 129.3, 129.6, 130.6, 144.5. MS (HR) for $C_{18}H_{19}N_3$ Calcd: 277.1579. Found: 277.1576.

2,5-Bis(4-N,N-dimethylaminophenylmethyl)pyrrole (3.21b). Obtained as an oil. ^1H NMR δ 2.85 (s, 12 H), 3.73 (s, 4 H), 5.78 (d, $J = 2.6$ Hz, 2 H), 6.62-6.65 (m, 4 H), 7.00-7.03 (m, 4 H), 7.45 (s, br, 1 H); ^{13}C NMR δ 32.9, 40.7, 105.8, 112.8, 127.7, 129.1, 130.6, 149.1.

Anal. Calcd for $C_{22}H_{27}N_3$: C, 79.24; H, 8.16. Found: C, 79.06; H, 8.11.

2,5-Bis(4-N,N-diethylaminophenylmethyl)pyrrole
(3.21c). Obtained as plates. ^1H NMR δ 1.13 (t, $J = 7.0$ Hz, 12 H), 3.26 (q, $J = 7.0$ Hz, 8 H), 3.77 (s, 4 H), 5.81 (d, $J = 2.6$ Hz, 2 H), 6.59–6.62 (m, 4 H), 7.00–7.03 (m, 4 H), 7.48 (s, br, 1 H); ^{13}C NMR δ 12.5, 33.0, 44.4, 105.8, 112.1, 126.5, 129.4, 130.8, 146.3.

Anal. Calcd for $C_{26}H_{35}N_3$: C, 80.16; H, 9.06; N, 10.79. Found: C, 79.79; H, 9.21; N, 10.55.

2,5-Bis(4-N,N-dimethylaminophenylmethyl)-N-methylpyrrole (3.21d). Obtained as plates. ^1H NMR δ 2.88 (s, 12 H), 3.19 (s, 3 H), 3.80 (s, 4 H), 5.78 (s, 2 H), 6.47 (d, $J = 8.8$ Hz, 4 H), 7.01 (d, $J = 8.8$ Hz, 4 H); ^{13}C NMR δ 30.4, 32.3, 40.8, 105.9, 112.8, 127.5, 129.0, 131.8, 149.1.

Anal. Calcd for $C_{23}H_{29}N_3$: C, 79.50; H, 8.41; N, 12.09. Found: C, 79.51; H, 8.61; N, 12.14.

1,1-Dibenzoyl-2-(4-N,N-dimethylaminophenyl)ethane
(3.22). A mixture of 4-(benzotriazol-1-ylmethyl)-N,N-dimethylaniline (3.12b) (0.63 g, 2.5 mmol), dibenzoylmethane (0.56 g, 2.5 mmol) and anhydrous zinc bromide (0.84 g, 3.75 mmol) in dry toluene was heated under reflux

for 27 h, then cooled, poured into aqueous NaOH solution (10%; 30 ml), extracted with ether (3 x 30 ml) and dried over MgSO₄. The solvent was evaporated, the residue chromatographed (see Table 3.3) then recrystallized from ethanol to give 3.22 (0.22 g, 25%) as needles. ¹H NMR δ 2.84 (s, 6 H), 3.37 (d, J = 6.6 Hz, 2 H), 5.51 (t, J = 6.6 Hz, 1 H), 6.60 (d, J = 8.8 Hz, 2 H), 7.11 (d, J = 8.8 Hz, 2 H), 7.3–7.5 (m, 6 H), 7.89–7.91 (m, 4 H); ¹³C NMR δ 34.2, 40.6, 59.4, 112.8, 126.8, 128.5, 128.7, 129.5, 133.3, 136.0, 149.3, 195.5.

3-(4-N,N-Dimethylaminophenyl)propiophenone (3.23a).

Obtained as an oil. ¹H NMR δ 2.86 (s, 6 H), 2.95 (t, J = 8.0 Hz, 2 H), 3.21 (t, J = 8.0 Hz, 2 H), 6.67 (d, J = 8.8 Hz, 2 H), 7.11 (d, J = 8.8 Hz, 2 H), 7.35–7.50 (m, 3 H), 7.91–7.94 (m, 2 H); ¹³C NMR δ 29.1, 40.6, 40.7, 112.9, 127.9, 128.4, 128.8, 129.1, 132.7, 136.8, 149.0, 199.4.

4-(4-N,N-Dimethylaminophenyl)-2-butanone (3.23b).

Obtained as plates (trituated with hexane). ¹H NMR δ 2.12 (s, 3 H), 2.65–2.82 (m, 4 H), 2.90 (s, 6 H), 6.68 (d, J = 8.7 Hz, 2 H), 7.05 (d, J = 8.7 Hz, 2 H); ¹³C NMR δ 28.8, 30.0, 40.8, 45.6, 112.9, 128.8, 128.9, 149.1, 208.5.

1-(4-N,N-Dimethylaminophenyl)-1-(4-N,N-diethylamino-phenyl)ethane (3.26). Obtained as an oil. ¹H NMR δ 1.12

(t, $J = 7.0$ Hz, 6 H), 1.55 (d, $J = 7.0$ Hz, 3 H), 2.88 (s, 6 H), 3.29 (q, $J = 7.0$ Hz, 4 H), 3.96 (q, $J = 7.0$ Hz, 1 H), 6.60 (d, $J = 8.8$ Hz, 2 H), 6.67 (d, $J = 8.8$ Hz, 2 H), 7.05 (d, $J = 8.8$ Hz, 2 H), 7.10 (d, $J = 8.8$ Hz, 2 H); ^{13}C NMR δ 12.6, 22.3, 40.9, 42.7, 44.3, 111.9, 112.8, 128.1, 128.2, 134.1, 135.7, 146.0, 148.9.

Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2$: C, 81.03; H, 9.52. Found: C, 81.44; H, 9.74.

3-[1-(4-N,N-Dimethylaminophenyl)ethyl]indole (3.27a).
Obtained as microcrystals. ^1H NMR δ 1.65 (d, $J = 7.0$ Hz, 3 H), 2.87 (s, 6 H), 4.28 (q, $J = 7.0$ Hz, 1 H), 6.67 (d, $J = 8.5$ Hz, 2 H), 6.89–7.41 (m, 7 H), 7.82 (s, br, 1 H); ^{13}C NMR δ 22.5, 35.8, 40.8, 110.9, 112.9, 119.0, 119.8, 120.9, 121.7, 122.1, 126.9, 128.0, 135.1, 136.6, 148.9.

Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.54; H, 7.66; N, 10.75.

4-[Benzyl(indol-3-yl)methyl]-N,N-dimethylaniline (3.27b). Obtained as microcrystals. ^1H NMR δ 2.82 (s, 6 H), 3.24 (dd, $J = 8.4, 13.6$ Hz, 1 H), 3.46 (dd, $J = 13.6, 6.8$ Hz, 1 H), 4.39 (dd, $J = 8.4, 6.8$ Hz, 1 H), 6.59 (d, $J = 8.5$ Hz, 2 H), 6.86–7.43 (m, 12 H), 7.71 (s, br, 1 H); ^{13}C NMR δ 40.7, 42.6, 43.7, 110.9, 112.7, 119.0, 119.6, 120.2, 121.4, 121.7, 125.6, 126.9, 127.9, 128.6, 129.0, 132.7, 136.4, 141.0, 148.9.

Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.11; N, 8.23.
Found: C, 84.65; H, 7.17; N, 8.00.

1-(4-Tolyl)-2-(4-N,N-dimethylaminophenyl)-2-(indol-3-yl)ethanol (3.27c). Obtained as microcrystals. ^1H NMR δ 2.26 (s, 3 H), 2.45 (s, br, 1 H), 2.81 (s, 6 H), 4.49 (d, $J = 8.0$ Hz, 1 H), 5.25 (d, $J = 8.0$ Hz, 1 H), 6.52 (d, $J = 8.8$ Hz, 2 H), 6.9-7.3 (m, 10 H), 7.47 (d, $J = 8.0$ Hz, 1 H), 8.10 (s, br, 1 H); ^{13}C NMR δ 21.1, 40.6, 50.7, 77.5, 111.0, 112.5, 115.8, 119.3, 119.5, 122.0, 122.4, 126.7, 127.6, 128.5, 129.2, 130.0, 136.3, 136.5, 139.7, 149.0.

Anal. Calcd for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56. Found: C, 80.81; H, 7.13; N, 7.43.

1-[(4-N,N-Dimethylaminophenyl)(indol-3-yl)methyl]cyclohexan-1-ol (3.27d). Obtained as microcrystals. ^1H NMR δ 1.20-1.72 (m, 10 H), 2.86 (s, 6 H), 4.21 (s, 1 H), 6.65 (d, $J = 8.5$ Hz, 2 H), 7.03-7.43 (m, 7 H), 7.62 (d, $J = 8.0$ Hz, 1 H), 8.09 (s, br, 1 H); ^{13}C NMR δ 22.3, 25.8, 36.7, 37.0, 40.7, 51.3, 73.9, 110.8, 112.5, 116.5, 118.9, 119.1, 121.6, 122.4, 128.4, 129.9, 130.1, 135.4, 149.1.

Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.10; N, 8.04. Found: C, 79.27; H, 8.07; N, 8.39.

1-(Pyrid-4-yl)-2-(4-N,N-dimethylaminophenyl)-2-(indol-3-yl)ethanol (3.27e). Obtained as microcrystals. ^1H

NMR δ 2.72 (s, br, 1 H), 2.86 (s, 6 H), 4.47 (d, J = 7.0 Hz, 1 H), 5.28 (d, J = 7.0 Hz, 1 H), 6.56 (d, J = 8.8 Hz, 2 H), 7.01–7.33 (m, 10 H), 7.43 (d, J = 7.6 Hz, 1 H), 8.28 (s, br, 1 H), 8.40 (d, J = 6.0 Hz, 2 H); ^{13}C NMR δ 40.6, 50.5, 76.5, 111.1, 112.6, 114.7, 119.3, 119.7, 121.7, 122.5, 127.4, 128.6, 129.2, 136.3, 149.2, 149.4, 151.7.

Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}$: C, 77.28; H, 6.49; N, 11.76. Found: C, 77.04; H, 6.64; N, 11.63.

2-(4-N,N-Dimethylaminophenyl)-2-(indol-3-yl)-1,1-diphenylethanol (3.27f). Obtained as plates. ^1H NMR δ 2.74 (s, 6 H), 3.03 (s, 1 H), 5.43 (s, 1 H), 6.38 (d, J = 8.6 Hz, 2 H), 6.77–7.32 (m, 16 H), 7.49 (d, J = 7.4 Hz, 1 H), 7.73 (s, br, 1 H); ^{13}C NMR δ 40.4, 50.6, 81.0, 110.7, 112.1, 115.3, 118.9, 119.0, 121.4, 125.0, 125.7, 125.9, 126.0, 126.3, 127.3, 127.6, 127.7, 130.6, 135.4, 146.5, 147.6, 149.0.

Anal. Calcd for $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}$: C, 83.30; H, 6.52; N, 6.48. Found: C, 83.04; H, 6.62; N, 6.29.

2-Phenyl-2-(4-N,N-dimethylaminophenyl)acetophenone (3.28). Obtained as plates. ^1H NMR δ 2.90 (s, 6 H), 5.93 (s, 1 H), 6.68 (d, J = 8.8 Hz, 2 H), 7.1–7.5 (m, 10 H), 8.00–8.02 (m, 2 H); ^{13}C NMR δ 40.5, 58.6, 112.8, 126.5, 126.8, 128.48, 128.5, 128.9, 129.1, 129.8, 132.7, 137.1, 140.0, 149.6, 198.7.

Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44.
Found: C, 83.41; H, 6.86; N, 4.35.

2-(4-N,N-Dimethylaminophenyl)-2-methoxy-1,1-diphenylethanol (3.29). Obtained as plates. ^1H NMR δ 2.86 (s, 6 H), 3.16 (s, 1 H), 3.26 (s, 3 H), 4.95 (s, 1 H), 6.50 (d, $J = 8.0$ Hz, 2 H), 6.86 (d, $J = 8.0$ Hz, 2 H), 7.0-7.4 (m, 8 H), 7.5-7.6 (m, 2 H); ^{13}C NMR δ 40.4, 56.5, 80.7, 86.5, 111.4, 123.6, 126.3, 126.4, 126.7, 127.1, 127.4, 127.8, 129.7, 144.1, 146.2, 149.9.

Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.11; H, 7.36; N, 3.92.

1,1-Diphenyl-2-(indol-3-yl)-2-(4-N,N-dimethylamino-phenyl)ethylene (3.30). Obtained as microcrystals. ^1H NMR δ 2.81 (s, 6 H), 6.4-7.3 (m, 17 H), 7.6-7.8 (m, 2 H), 8.0 (s, br, 1 H); ^{13}C NMR δ 40.3, 110.7, 111.5, 119.2, 119.6, 121.0, 121.4, 125.5, 126.6, 127.4, 127.5, 127.6, 128.0, 130.8, 131.1, 131.6, 132.0, 134.0, 135.7, 137.6, 144.7, 145.8, 148.8.

Anal. Calcd for $C_{30}H_{26}N_2$: C, 86.92; H, 6.32; N, 6.76.
Found: C, 86.52; H, 6.32; N, 6.57.

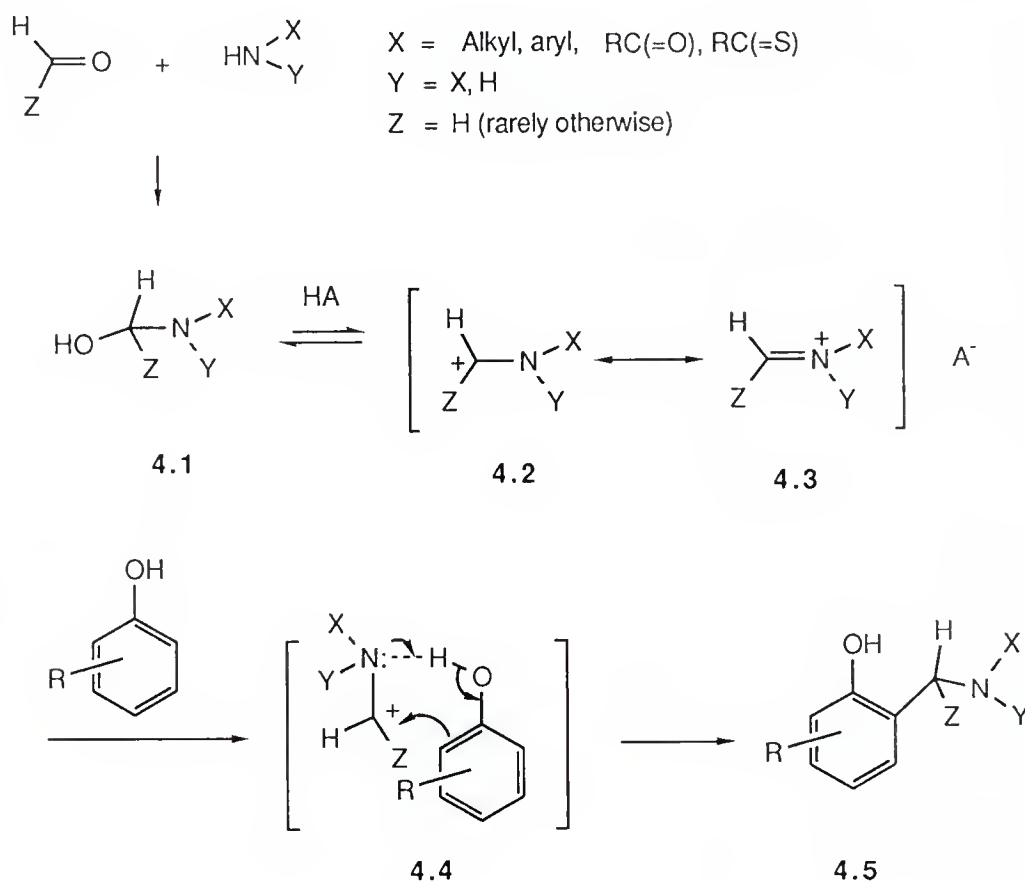
CHAPTER IV
o-(α -BENZOTRIAZOLYLALKYL)PHENOLS:
VERSATILE INTERMEDIATES FOR SYNTHESIS OF
SUBSTITUTED PHENOLS

4.1 Introduction

4.1.1 α -Amidoalkylation of Phenols

Classical Mannich reactions condense active CH-compounds, including phenols, with formaldehyde and an amine [42OR303, 73S703, 90T1791]. Important extensions of Mannich reactions in which amides, imides, ureas, thioureas, etc. replace the amine component are well documented in the literature [63MI1, 65OR52, 70S49, 76AG909, 73S243, 84S85]. Phenols have been employed as active CH-compounds in such Mannich condensations with aldehydes and amides or imides under various conditions. The ortho-substituted derivative is obtained unless both ortho positions are occupied, in which case the Mannich reaction occurs at the para-position [57RTC249]. Zaugg [63JOC2925] attributed the high ortho- to para- preference to the assistance of the phenolic hydroxyl group. The first step is the addition of the NH group to the carbonyl carbon of formaldehyde (or rarely other aldehydes) giving rise to an α -alkylol compound 4.1 (Scheme 4.1). Compound

4.1 is converted (generally via acid catalysis) into a carbonium/imonium ion (4.2 $\leftrightarrow$ 4.3) which then reacts with the phenol to yield the condensation product 4.5. A quasi six-membered chelate ring 4.4 preceding the carbon carbon bond formation is believed to be responsible for the preferred ortho-substitution of phenols [61JOC4078, 64TL1353].



Scheme 4.1

Compounds 4.1 can be isolated prior to use. An example is the Tseherniac-Einhorn reaction [69JOC14], where N-hydroxymethylphthalimide is the electrophilic reagent in the aromatic substitution process. Other analogous reagents that have been isolated prior to use are N-alkoxyalkylamides [66JOC133], N-haloalkylamides [63JOC2925], and N,N'-(arylmethylene)bisamides [57RTC249]. In most of these cases the carbonyl compound has been formaldehyde.

4.1.2 Importance and Synthesis of Phenols

Phenols represent a class of compounds which has found numerous applications in the transformation of organic compounds and in industry. Many natural products, such as lignans and neolignans, as well as alkaloids which possess phenolic fragments, have been synthesized by phenolic oxidation or by anodic oxidation of phenols as the key step. These biosynthetic methods have been subject to several reviews [72S657, 82CSR75, 85MI1, 88MI2]. On the other hand, the Mannich bases derived from phenols are versatile synthons which are widely employed in diverse types of organic transformations [73S703]. Also, quinone methides from phenol derivatives play an important role in biosynthesis and in the biological activity of many quinonoid antitumor compounds. They are very reactive and unstable and have proven very valuable as intermediates

especially for the construction of condensed benzopyran rings [74MI3, 80JOC3726].

Phenols have also long been used in the fragrance and flavor industries, and this is well documented in the literature [68MI1, 68MI2, 71MI1, 80MI3]. Reactions between phenols and formaldehyde under strictly controlled conditions give phenolic alcohols of low molecular weight which serve as starting materials for the synthesis of phenolic aldehydes. These phenolic aldehydes such as vanillin (4-hydroxy-3-methoxybenzaldehyde) are the intermediates from which a large number of important fragrance and flavor substances are derived.

The usual methods for the preparation of alkyl phenols are based upon the reactions of alcohols, alkyl halides, and alkenes with phenols in the presence of acid catalysts [49OR58, 63MI2]. Generally, o-mono or o,p-di substituted phenols are obtained; if the p- position is blocked, substitution occurs at the o- position. In particular, under Friedel-Crafts conditions, the reactions of phenols with alkyl halides usually afforded p-isomers [30JA4484, 31JA2379, 32JA1506]. The preparation of substituted phenols was also achieved by Claisen rearrangement of phenol ethers [44OR1] and by reduction of Mannich bases from phenols [42OR303, 88SC1207]. A recent report appeared in which phenol was acylated with acyl chloride under Friedel-Crafts conditions to give ketones,

followed by Wolff-Kishner reduction to give *p*-substituted phenols [76MI1].

4.1.3 Aim of the Work

Previous work described in Chapter II and Chapter III has investigated the use of benzotriazole in certain aromatic substitutions. Anilines were readily alkylated with 1-hydroxymethylbenzotriazole (4.10) to afford 4.6 which in turn underwent smooth lithiation and subsequent reaction with an electrophile at the methylene carbon to give derivatives 4.7. The displacement of the benzotriazole group in compounds 4.6 and 4.7 by anilines and other electron-rich aromatic compounds such as indoles, pyrroles, etc. gave diarylmethanes (4.8; E = H) and trisubstituted methanes (4.8; E $\neq$ H), respectively.

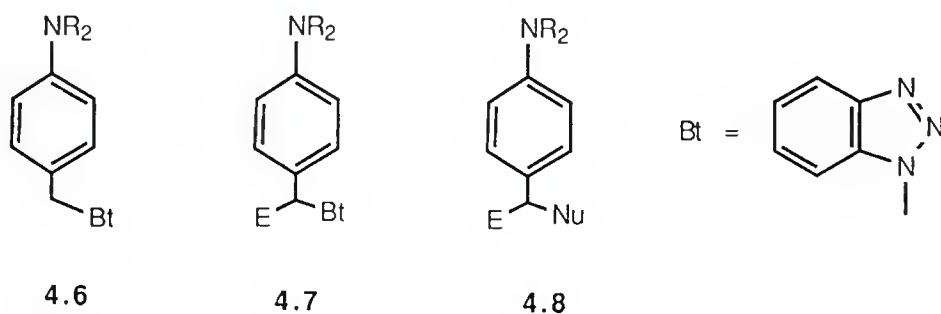


Figure 4.1 Benzotriazolyl Aniline Derivatives and Their Displacement Products

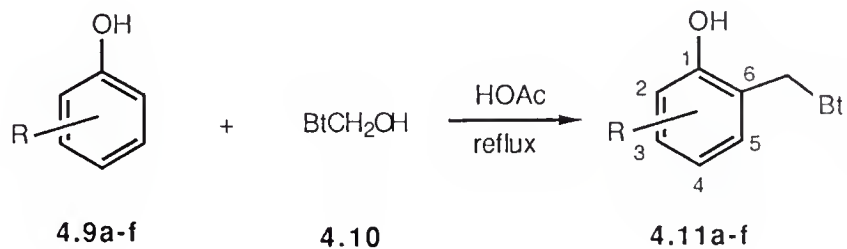
The displacement of the benzotriazole group is assisted by the electron pair from the amino nitrogen atom. We believe that the similar alkylation of phenols with 1-hydroxymethylbenzotriazole (4.10) should occur, and that the subsequent displacement of benzotriazole would also be assisted by the phenolic oxygen lone pair, or even by the phenolate ion, in a manner similar to that established for the aniline system. Thus, the objective of the present work is to investigate the use of benzotriazole as a synthetic auxiliary in the phenol system and thus to develop a new methodology for the convenient synthesis of substituted phenols.

4.2 Results and Discussion

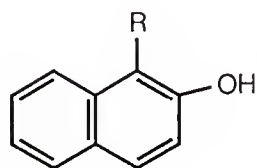
4.2.1 Reactions of Phenols with 1-Hydroxymethylbenzotriazole

A series of phenols and naphthols 4.9a-h, unsubstituted at the ortho position, when heated with 1-hydroxymethylbenzotriazole (4.10) in acetic acid under reflux, afforded the corresponding ortho substituted products 4.11a-h in moderate to excellent yields. Protonation at the oxygen atom in 4.10, followed by loss of water would give rise to reactive cations (4.13 $\leftrightarrow$ 4.14). Hydrogen bonding between the phenolic hydrogen and the basic nitrogen of the benzotriazole group would lead

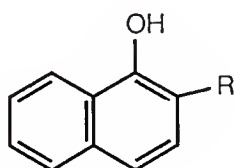
to ortho substitution. Other mechanisms could also be proposed to explain the formation of compounds 4.11.



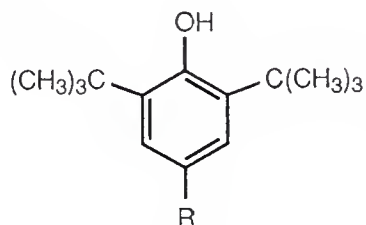
4.9,4.11	a	b	c	d	e	f
R	H	2-Me	4-Me	2- ^t Bu	2- ^t Bu-4-Me	4-C ₁₂ H ₂₅



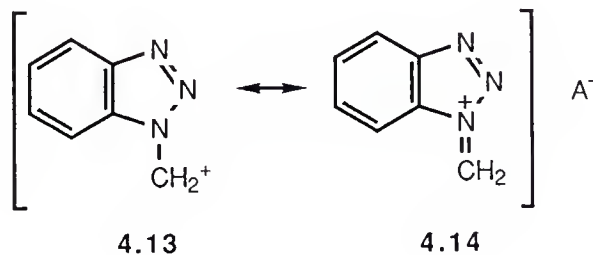
4.9g R = H
4.11g R = CH₂Bt



4.9h R = H
4.11h R = CH₂Bt



4.9i R = H
4.12 R = CH₂Bt



Scheme 4.2

In the example of 2,6-di-tert-butylphenol 4.9i, where both o-positions were blocked, more vigorous reaction conditions forced the alkylation to the para- position. On heating with 4.10 under reflux in toluene, in the presence of one equivalent of p-toluenesulfonic acid monohydrate for two days, the para-alkylated product 4.12 was obtained in a yield of 50%.

Table 4.1 Preparation of (Benzotriazol-1-ylmethyl)phenols 4.11 and 4.12

Comp.	Reaction time (h)	Yield ^a (%)	M.p. (°C)	Product isolation ^b
4.11a	72	55	168-170	2:1 ^c
4.11b	72	59	156-158	2:1 ^c
4.11c	72	43	140-142	2:1 ^c
4.11d	45	71	108-110	2:1 ^c
4.11e	42	66	132-134	Et ₂ O/hexane ^d
4.11f	48	46	87-91	6:1 ^e
4.11g	24	93	219-221	Et ₂ O ^d
4.11h	4	41	172-174	2:1 ^e
4.12	48	50	134-136	9:1 ^e

^a Isolated yields.

^b Isolation of products. Further purification for the analytically pure sample is described for the particular compound.

^c Trituration of the crude product with Et₂O/hexane gave the desired products. Additional products were obtained by column chromatography. The ratio indicated that of eluent, hexane/EtOAc, v/v.

^d Trituration solvent.

^e The crude product was directly chromatographed. The ratio indicated that of eluent, hexane/EtOAc, v/v.

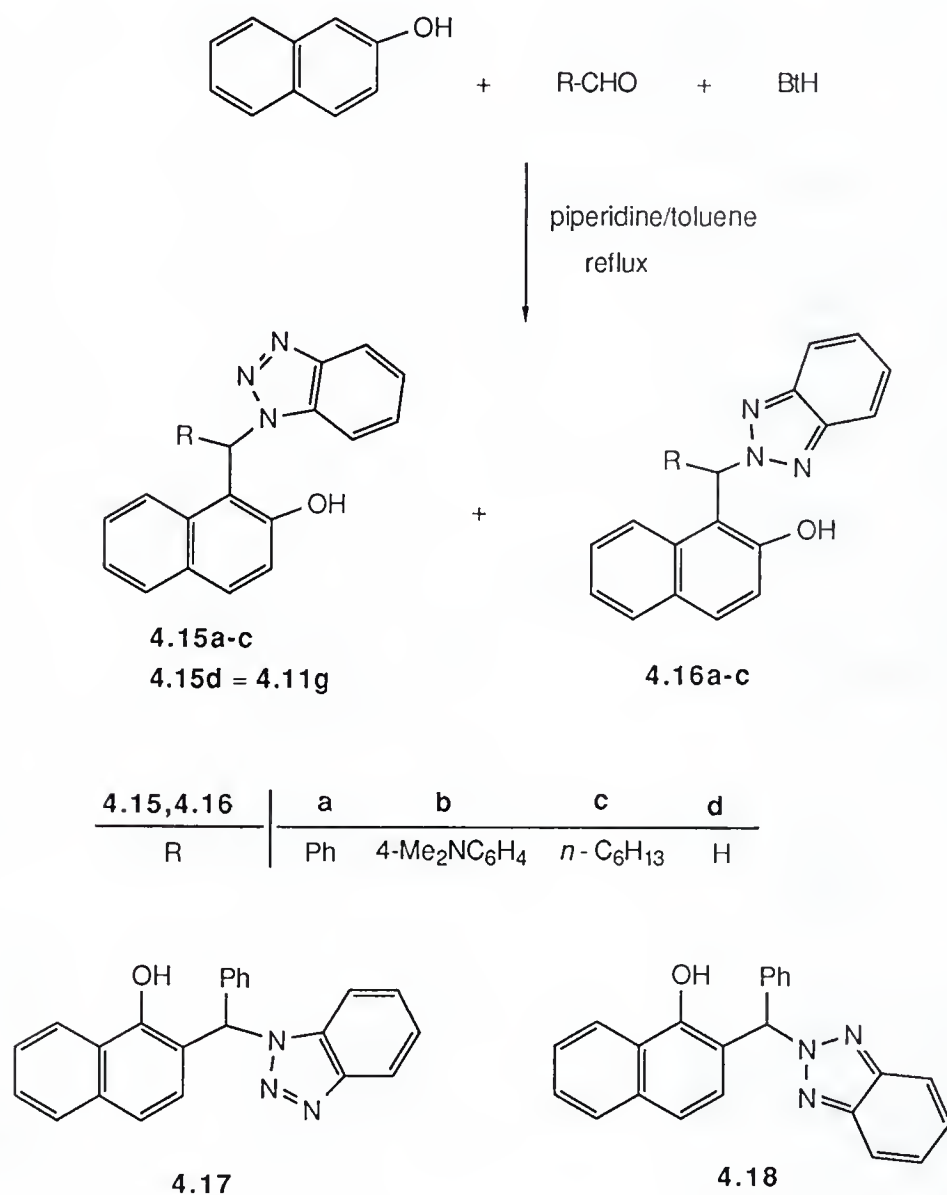
4.2.2 Reactions of Naphthols with Benzotriazole and Other Aldehydes

Attempts to condense phenol with benzaldehyde and benzotriazole in the presence of *p*-toluenesulfonic acid, piperidine, or 4-dimethylaminopyridine failed even under reflux in toluene for three days. The NMR spectra of the crude product displayed complex mixtures in which the unreacted benzotriazole and phenol resonances were predominant. The absence of the aliphatic Bt-CH signal in the ^{13}C NMR spectra indicated that the expected product was not formed.

However, the high reactivity of 2-naphthol enabled it to react with aromatic aldehydes and benzotriazole in high yields to afford mixtures of 1- and 2-(benzotriazolyl) isomers 4.15a-b and 4.16a-b, respectively. The condensation with formaldehyde, on the other hand, gave exclusively the 1-isomer 4.11g. The two isomers 4.15 and 4.16 were separated by a combination of recrystallization and column chromatography (see section 4.4, Experimental). The isomer ratio isolated was found to be dependent on the reflux time. With benzaldehyde, a reflux time of 24 h gave the 1-isomer 4.15a and the 2-isomer 4.16a in a ratio of 3:4. Shorter reflux times (e.g. 2 h) afforded the 1-isomer 4.15a as the predominant product in the ratio of 7:2. The condensation with *n*-heptaldehyde and benzotriazole over 23 hrs gave the 1-isomer 4.15c (10%) and the 2-isomer 4.16c

(15%) while unreacted 2-naphthol was recovered in 52% yield.

1-Naphthol also condensed with benzaldehyde and benzotriazole to give a mixture of the 1- and 2- isomers 4.17 and 4.18 in yields of 34% and 23%, respectively.



Scheme 4.3

Table 4.2 Preparation of (Benzotriazol-1-ylalkyl)naphthols

Comp.	Reaction time (h)	Yield ^a (%)	M.p. (°C)
4.11g	24	91	219-221
4.15a	2	71	240-242
4.15a	24	38	
4.16a	2	20	143-145
4.16a	24	51	
4.15b	22	63	174-176
4.16b	22	23	186-188
4.15c	23	10	155-157
4.16c	23	15	143-145
4.17	4	34	147-149
4.18	4	23	68-70

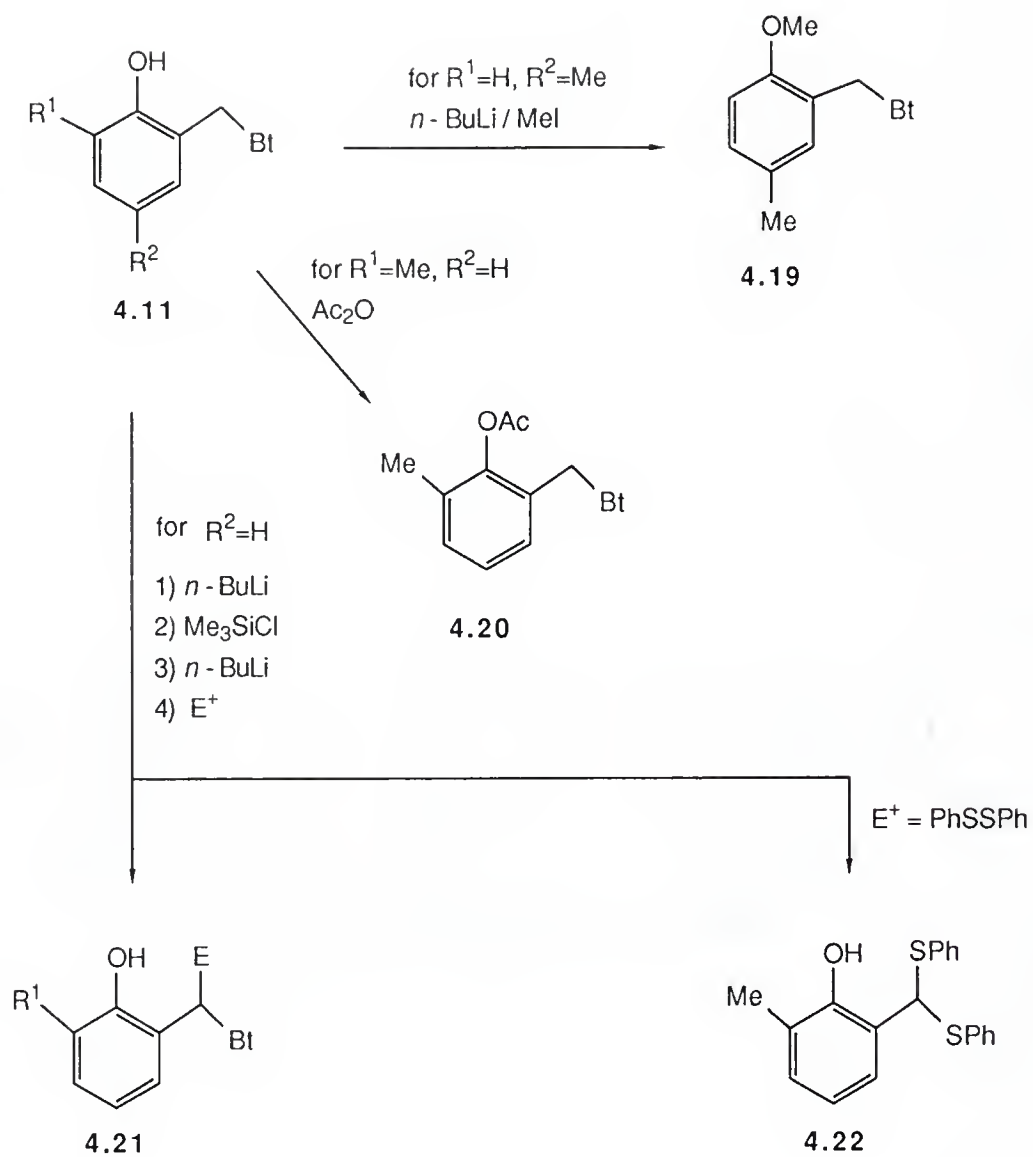
^a Isolated yields.

4.2.3 Lithiation of the Phenol Derivatives 4.11

Heteroatom assisted lithiation has received considerable attention recently due to its large synthetic utility [79OR1]. The phenolic hydroxyl group is relatively ineffective in directing ortho lithiation [54OR258, 79OR1, 83JA7790, 83S957]. Posner [85JA2571] succeeded in the

ortho lithiation of phenol by employing tert-butyllithium in tetrahydropyran (THP): the dianion was trapped by various electrophiles to give the C-alkylated products (with trimethylsilyl chloride, the O,C-disilylated product was observed). However, Morey et al. [90JOC3902] found that the alkoxy groups usually determined the regioselectivity in the lithiation of alkoxyphenols. MNDO calculations [90JOC3902] suggest that phenol lithiations are highly dependent on the reaction conditions.

With compounds of type 4.11, the methylene groups are doubly activated: they are benzylic and also attached to an electron-withdrawing benzotriazole group. Nevertheless, 4.11c in THF at -78 °C on treatment successively with two equivalents of n-butyllithium and one equivalent of methyl iodide gave a mixture of starting material 4.11c (24%) and 2-(benzotriazol-1-ylmethyl)-4-methylanisole (4.19) through O-alkylation (28%). C-Alkylation was still not achieved when the hydroxy group of 4.11b was protected as its acetyl derivative 4.20. Posner's conditions [85JA2571] yielded a 1:1 ratio of unreacted 4.11b and the C-methylation product 4.21b. However, when 4.11b in THF was treated successively with equimolar amounts of n-butyllithium, trimethylsilyl chloride, n-butyllithium and finally an electrophile under carefully controlled conditions (*vide infra*), good yields of C-alkylation products were obtained. Work-up with ethanolic hydrochloric acid, which



4.21	a	b	c	d	e	f
R ¹	H	Me	Me	Me	Me	Me
E	PhCH(OH)	Me	<i>n</i> -Bu	CO ₂ H	Ph ₂ C(OH)	PhS

Scheme 4.4

removed the protecting trimethylsilyl group, afforded the desired products 4.21b-e. Phenyl disulfide gave the bis(phenylthio) product 4.22, evidently formed by the displacement of benzotriazole from the initial product 4.21f by a phenylthiol anion. Reaction of the phenol derivative 4.11a with benzaldehyde gave the desired product 4.21a in a yield of 68% (Table 4.3).

Table 4.3 Lithiation of Compounds 4.11

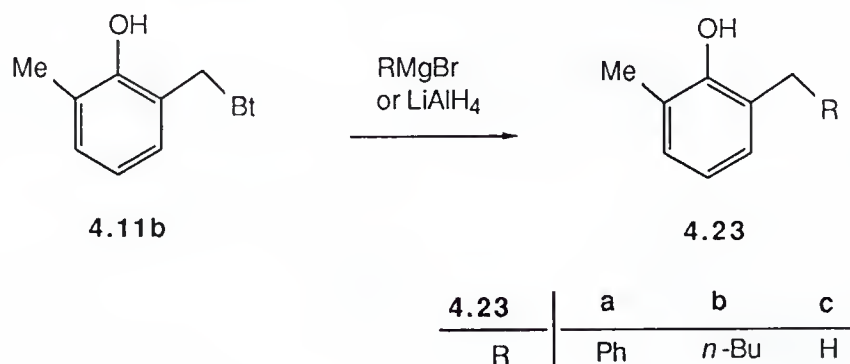
Pro- duct	Electro- phile	Sub- strate	Isolated yield (%)	M.p. (°C)
4.21a	PhCHO	4.11a	68	153-155
4.21b	MeI	4.11b	71	157-159
4.21c	<u>n</u> -BuI	4.11b	50	125-127
4.21d	CO ₂	4.11b	71	188-190
4.21e	Ph ₂ CO	4.11b	62	246-248

4.2.4 Displacement of the Benzotriazole Group

The benzotriazole group in compounds of type Bt-CRR'Z with Z = NR₂, OR, and SR have been displaced by Grignard

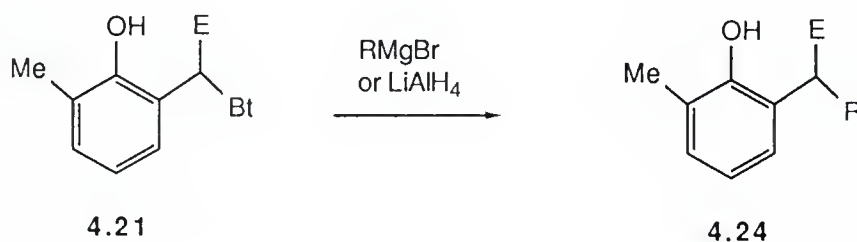
or organolithium reagents or by hydride ion to yield amines [89JCS(P1)225 and the references therein], ethers [89JOC6022], or thioethers [91UP1], respectively. We speculated that the hydroxy group, after deprotonation, should activate the phenol ring and assist the removal of the benzotriazole group to form quinone methide intermediates, which upon addition of nucleophiles should then lead to substituted phenols.

Phenylmagnesium bromide in refluxing diethyl ether, tetrahydrofuran, or 1,2-dimethoxyethane did not react with 4.11b. However, heating 4.11b with phenylmagnesium bromide or *n*-butylmagnesium bromide in toluene under reflux (as previously used in the reaction of benzotriazolyl alkoxy adducts with Grignard reagents [89JOC6022]) afforded the desired products 4.23a,b. Compound 4.11b was also reduced by lithium aluminum hydride in refluxing toluene to give 2,6-dimethylphenol (4.23c) (Scheme 4.5).



Scheme 4.5

As expected, substituents on the methylene carbon increase the reactivity. Thus the methylated substrate **4.21b** reacted with phenyl- and benzyl-magnesium bromides in THF under reflux to give the desired products **4.24a-b**. Lithium aluminum hydride reduced **4.21b-c** into **4.24c** and **4.23b** in good yields (Scheme 4.6).

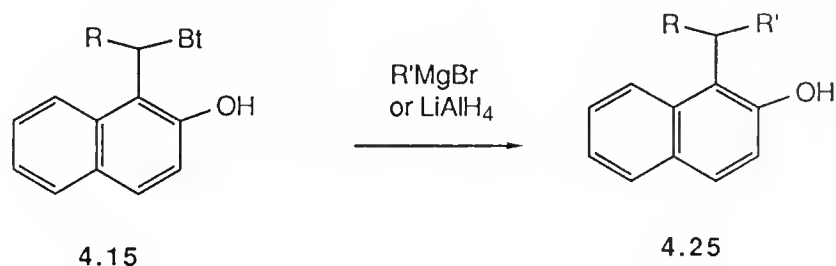


4.24	a	b	c	4.23b
E	Me	Me	Me	<i>n</i> -Bu
R	Ph	PhCH ₂	H	H

Scheme 4.6

In **4.15a**, the presence of the phenyl substituent enabled the reactions with Grignard reagents to occur at room temperature. Compound **4.15b** is even more reactive; the Grignard reaction had to be carried out at $-78\text{ }^{\circ}\text{C}$ to prevent decomposition. Lithium aluminum hydride converted

4.15a-b in refluxing THF into the corresponding reduced products 4.25a-b in good yields (Scheme 4.7 and Table 4.4).



4.25	a	b	c	d	e	f
R	Ph	4-Me ₂ NC ₆ H ₄	Ph	Ph	4-Me ₂ NC ₆ H ₄	4-Me ₂ NC ₆ H ₄
R'	H	H	Ph	PhCH ₂	Ph	PhCH ₂

Scheme 4.7

4.2.5 NMR Spectra of (α -Benzotriazolylalkyl)phenols

The structures of the products 4.11-4.12 and 4.15-4.18 are confirmed by ^1H and ^{13}C NMR spectroscopy and by elemental analyses. The ^{13}C NMR spectra of compounds 4.11-4.12, 4.15, and 4.17 display the characteristic pattern for the 1-substituted benzotriazoles. The quaternary carbons, $\underline{\text{C}}\text{-3a}$ and $\underline{\text{C}}\text{-7a}$ of the benzotriazole moiety

Table 4.4 Displacement of Benzotriazole By Grignard Reagents and LiAlH₄

Prod.	Substrate	Reagent	React. time (h)	Yield ^a (%)	M.p. °C	Purif. solvent ^b
4.22	4.21f	PhS	12	77	oil	30:1
4.23a	4.11b	PhMgBr	72	45	oil ^c	- ^d
4.23b	4.11b	<u>n</u> -BuMgBr	24	29	oil	50:1
4.23b	4.21c	LiAlH ₄	48	62	oil	50:1
4.23c	4.11b	LiAlH ₄	48	50	46-48 ^e	50:1
4.24a	4.21b	PhMgBr	17	80	oil ^f	20:1
4.24b	4.21b	PhCH ₂ MgBr	12	66	oil	30:1
4.24c	4.21b	LiAlH ₄	48	59	oil ^g	50:1
4.25a	4.15a	LiAlH ₄	22	90	112-114 ^h	10:1
4.25b	4.15b	LiAlH ₄	3	94	145-147 ⁱ	10:1
4.25c	4.15a	PhMgBr	22	66	106-108 ^j	10:1
4.25d	4.15a	PhCH ₂ MgBr	3	86	oil	10:1
4.25e	4.15b	PhMgBr	12	68	187-189	12:1
4.25f	4.15b	PhCH ₂ MgBr	2	90	118-120	10:1

^a Isolated yields.^b Initial purification for isolation of the products. Further purification for the preparation of analytically pure samples is described in the Experimental section. The ratio indicates that of the eluent used for column chromatography (petroleum ether (38-56 °C)/EtOAc, v/v).^c Lit. [58JOC9] m.p. 52°C.^d The crude product was chromatographed with hexane to methylene chloride, 1:1, v/v.^e Lit. [40JA2091] m.p. 48-49°C.^f Lit. [57AG699] b.p. 166°C/10 torr.^g Lit. [26LA162] b.p. 212-214°C.^h Lit. [76JCS(P1)2570] m.p. 110-111.5°C.ⁱ Lit. [34JCS1136] m.p. 143°C.^j Lit. [60JOC2223] m.p. 109°C.

resonate between 144.4–146.2 ppm and between 131.7–133.4 ppm, respectively. The methylene carbons in compounds 4.11 (except for the naphthol analogs 4.11g, 4.11h) give signals in the region 46.4–48.6 ppm which are shifted upfield due to the mesomeric and steric effects [78OMR607] as compared to the para-substituted derivative 4.12 (52.6 ppm). The methylene protons of 4.11a–f are observed at 5.75–6.00 ppm. For the naphthyl analogues 4.11g–h, the methylene protons resonate downfield at 6.35 and 6.08 ppm, respectively. While the chemical shift of the methylene carbon of 4.11h is comparable to those of the phenyl derivatives 4.11a–f, the methylene carbon of 4.11g is shifted upfield due to the steric effect (42.6 ppm) [78OMR607] (see Table 4.5). For the 1-isomers 4.15 and 4.17, due to the presence of an extra substituent attached to the methylene carbon, both the α -proton and the α -carbon (see Table 4.5) resonances are shifted downfield as compared to the methylene protons and carbons in 4.11 and 4.12. For the 2-isomers 4.16 and 4.18, while the α -proton resonances are comparable to those of the corresponding 1-isomers, the α -carbon resonances are shifted further downfield than those of the 1-isomers due to the presence of two electron-withdrawing N=C bonds.

Table 4.5 ^1H and ^{13}C NMR Chemical Shifts of Methylene or Methine Groups, and ^{13}C NMR Chemical Shifts of C-3a and C-7a of Benzotriazole in 4.11-4.12, 4.15-4.18 (ppm)

Compound	$\delta_{\text{H}}(\underline{\text{CH}_2})$ (R_3CH)	$\delta_{\text{C}}(\underline{\text{CH}_2})$ (R_3CH)	$\delta_{\text{C}}(\underline{\text{C}}-7\text{a})$	$\delta_{\text{C}}(\underline{\text{C}}-3\text{a})$
4.11a	5.91	46.5	132.9	145.3
4.11b	5.92	47.0	132.9	145.2
4.11c	5.83	46.4	132.8	145.2
4.11d	5.75	48.6	132.5	145.6
4.11e	6.00	46.9	132.8	145.3
4.11f	5.95	47.7	132.9	145.4
4.11g	6.35	<u>42.6</u>	132.6	145.2
4.11h	6.08	46.1	131.8	144.8
4.12	5.74	<u>52.6</u>	132.8	146.2
4.15a	8.31	57.9	132.2	144.8
4.15b	8.17	58.1	131.7	144.4
4.15c	6.85	56.2	132.3	145.5
4.17	7.74	62.5	133.4	145.0
4.16a	8.36	66.6		143.5
4.16b	8.33	66.6		143.4
4.16c	6.96	63.0		143.1
4.18	7.50	73.9		143.5

4.3 Conclusions

Phenols and naphthols are benzotriazolylmethylated by 1-hydroxymethylbenzotriazole (a formaldehyde derivative) at the o- (or if both o-positions are occupied at the p-) position. The reaction can be extended to other aldehydes in the case of the naphthols. The methylene group in the o-(benzotriazolylmethyl)phenols can be lithiated (but only after trimethylsilyl protection of the hydroxyl) and then substituted by various electrophiles. The benzotriazole residues in both the primary products and in their substituted derivatives can be displaced by the alkyl anions of Grignard reagents or by the hydride ion of lithium aluminum hydride allowing the synthesis of many new types of substituted phenols.

4.4 Experimental

The apparatus and general procedures applied in this Chapter are identical to those described in Chapter II and III with the following additions.

Column chromatography was carried out on silica gel (MBA, 230-400 mesh).

1-Hydroxymethylbenzotriazole (4.10) was prepared according to the modified literature procedure, m.p. 149-151 °C (lit. [52JA3868] m.p. 148-151 °C).

4.4.1 General Procedure for the Alkylation of Phenols:
Preparation of o-(Benzotriazol-1-ylmethyl)phenols
(4.11)

A mixture of 1-hydroxymethylbenzotriazole (4.10) (3.75 g, 25 mmol) and the corresponding phenol (25 mmol) in acetic acid (25 ml) was heated under reflux for the appropriate time (see Table 4.1). The acetic acid was removed under reduced pressure and to the residue was added sodium hydrogen carbonate solution (10%; 30 ml). The product was extracted with diethyl ether (3 × 30 ml), washed with water, and the organic extracts dried (MgSO₄). The solvent was removed in vacuo to give the crude products. Physical data of the products, methods of isolation, reaction time, and yields are given in Table 4.1. Further purification for the preparation of the analytically pure sample is described for the individual compound.

2-(Benzotriazol-1-ylmethyl)phenol (4.11a). Obtained as plates (recrystallized from methanol/EtOAc). ¹H NMR (DMSO-d₆) δ 5.91 (s, 2 H), 6.78 (t, J = 7.0 Hz, 1 H), 6.94 (d, J = 8.0 Hz, 1 H), 7.1–7.2 (m, 2 H), 7.38 (t, J = 7.0 Hz, 1 H), 7.51 (t, J = 7.0 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 1 H), 8.07 (d, J = 8.0 Hz, 1 H), 10.00 (s, 1 H); ¹³C NMR (DMSO-d₆) δ 46.5, 110.9, 115.4, 119.1, 119.2, 121.8, 123.8, 127.1, 129.5, 129.7, 132.9, 145.2, 155.2.

Anal. Calcd for C₁₃H₁₁N₃O: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.14; H, 4.93; N, 18.58.

2-(Benzotriazole-1-ylmethyl)-6-methylphenol (4.11b).

Obtained as microcrystals (recrystallized from methanol).

^1H NMR ($\text{DMSO}-d_6$) δ 2.20 (s, 3 H), 5.92 (s, 2 H), 6.74 (t, $J = 7.0$ Hz, 1 H), 6.90 (d, $J = 7.0$ Hz, 1 H), 7.05 (d, $J = 7.0$ Hz, 1 H), 7.38 (t, $J = 7.0$ Hz, 1 H), 7.51 (t, $J = 7.0$ Hz, 1 H), 7.79 (d, $J = 8.0$ Hz, 1 H), 8.05 (d, $J = 8.0$ Hz, 1 H), 8.90 (s, 1 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 16.6, 47.0, 110.9, 119.1, 119.6, 122.8, 123.8, 125.1, 127.1, 127.2, 130.9, 132.9, 145.2, 153.0.

Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}$: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.44; H, 5.49; N, 17.28.

2-(Benzotriazole-1-ylmethyl)-4-methylphenol (4.11c).

Obtained as microcrystals (recrystallized from methanol).

^1H NMR ($\text{DMSO}-d_6$) δ 2.12 (s, 3 H), 5.83 (s, 2 H), 6.8–6.9 (m, 3 H), 7.38 (t, $J = 8.0$ Hz, 1 H), 7.51 (t, $J = 8.0$ Hz, 1 H), 7.80 (d, $J = 8.0$ Hz, 1 H), 8.04 (d, $J = 8.0$ Hz, 1 H), 9.72 (s, 1 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 20.0, 46.4, 110.9, 115.3, 119.0, 121.4, 123.8, 127.0, 127.7, 129.9, 130.1, 132.8, 145.2, 152.9.

Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}$: C, 70.28; H, 5.48; N, 17.56. Found: C, 69.91; H, 5.44; N, 17.30.

2-(Benzotriazol-1-ylmethyl)-6-tert-butylphenol

(4.11d). Obtained as prisms (recrystallized from

hexane/EtOAc). ^1H NMR δ 1.41 (s, 9 H), 5.75 (s, 2 H), 6.84

(t, $J = 7.6$ Hz, 1 H), 7.17 (dd, $J = 7.5, 1.6$ Hz, 1 H), 7.28 (dd, $J = 8.0, 1.6$ Hz, 1 H), 7.36 (dt, $J = 7.0, 1.0$ Hz, 1 H), 7.50 (dt, $J = 7.0, 1.0$ Hz, 1 H), 7.63 (d, $J = 8.4$ Hz, 1 H), 7.76 (s, 1 H), 8.02 (d, $J = 8.4$ Hz, 1 H); ^{13}C NMR δ 29.7, 34.8, 48.6, 109.4, 120.1, 120.4, 122.4, 124.4, 128.0, 128.1, 128.2, 132.5, 139.1, 145.6, 154.4.

Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.74; H, 6.93; N, 15.14.

2-(Benzotriazol-1-ylmethyl)-6-tert-butyl-4-methylphenol (4.11e). Obtained as needles (recrystallized from hexane/EtOAc). ^1H NMR ($\text{DMSO}-d_6$) δ 1.40 (s, 9 H), 2.08 (s, 3 H), 6.00 (s, 2 H), 6.5–6.6 (m, 1 H), 6.9–7.0 (m, 1 H), 7.38 (t, $J = 8.0$ Hz, 1 H), 7.51 (t, $J = 8.0$ Hz, 1 H), 7.75 (d, $J = 8.0$ Hz, 1 H), 8.07 (d, $J = 8.0$ Hz, 1 H), 8.63 (s, 1 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 20.5, 29.8, 34.5, 46.9, 110.6, 119.2, 123.9, 124.6, 126.8, 127.2, 128.7, 132.8, 138.9, 145.3, 150.8.

Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.27; H, 7.27; N, 14.36.

2-(Benzotriazol-1-ylmethyl)-4-dodecylphenol (4.11f). Obtained as microcrystals (recrystallized from hexane). ^1H NMR δ 0.6–1.7 (m, 25 H), 5.95 (s, 2 H), 7.0–7.4 (m, 5 H), 7.6–7.8 (m, 1 H), 8.0 (d, $J = 7.0$ Hz, 1 H), 8.7 (broad, 1 H); ^{13}C NMR δ 8.5, 12.1, 14.0, 14.1, 14.7, 22.5, 22.6,

29.0, 35.5, 36.9, 37.1, 40.3, 47.6, 110.7, 116.0, 119.2, 120.2, 120.3, 124.2, 127.3, 127.5, 128.1, 132.9, 145.4, 152.4.

Anal. Calcd for $C_{25}H_{36}N_3O$: C, 76.10; H, 9.20; N, 10.65. Found: C, 75.72; H, 9.11; N, 10.94.

1-(Benzotriazol-1-ylmethyl)-2-naphthol (4.11g).

Obtained as plates (recrystallized from methanol). ^1H NMR (DMSO- d_6) δ 6.35 (s, 2 H), 7.1-7.5 (m, 5 H), 7.6-7.8 (m, 4 H), 8.28 (d, $J = 8.0$ Hz, 1 H), 10.63 (s, 1 H); ^{13}C NMR (DMSO- d_6) δ 42.6, 110.7, 111.6, 118.0, 119.1, 122.4, 122.9, 123.8, 127.0, 127.1, 128.2, 130.7, 132.6, 133.2, 133.4, 145.2, 153.9.

Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.15; H, 4.73; N, 15.20.

2-(Benzotriazol-1-ylmethyl)-1-naphthol (4.11h).

Obtained as prisms (recrystallized from hexane/EtOAc). ^1H NMR δ 6.08 (s, 2 H), 7.2-7.5 (m, 6 H), 7.63-7.73 (m, 2 H), 7.96 (dd, $J = 8.2, 1.0$ Hz, 1 H), 8.3-8.4 (m, 1 H), 9.59 (broad, 1 H); ^{13}C NMR δ 46.1, 109.5, 115.2, 118.3, 119.2, 121.4, 122.8, 124.3, 124.5, 125.4, 125.9, 126.1, 126.7, 131.8, 133.4, 144.8, 149.7.

Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.16; H, 4.69; N, 15.10.

4-(Benzotriazol-1-ylmethyl)-2,6-di-tert-butylphenol
 (4.12). A mixture of 2,6-di-tert-butylphenol (2.06 g, 10 mmol), 1-hydroxymethylbenzotriazole (1.49 g, 10 mmol), and p-toluenesulfonic acid monohydrate (1.90 g, 10 mmol) in toluene (30 ml) was heated under reflux for two days. Toluene was then removed under reduced pressure, the residue was washed with saturated sodium hydrogen carbonate solution (30 ml), extracted with diethyl ether (3 x 50 ml), and the organic extracts dried (MgSO₄). The solvent was removed in vacuo, and the residue isolated (see Table 4.1) to give 4.12 (1.68 g, 50%) as micro-crystals. ¹H NMR δ 1.38 (s, 18 H), 5.27 (s, 1 H), 5.74 (s, 2 H), 7.16 (s, 2 H), 7.3–7.5 (m, 3 H), 8.06 (d, J = 8.0 Hz, 1 H); ¹³C NMR δ 30.1, 34.2, 52.6, 109.8, 119.9, 123.7, 124.8, 125.4, 127.1, 132.8, 136.4, 146.2, 153.9.

Anal. Calcd for C₂₁H₂₇N₃O: C, 74.74; H, 8.06; N, 12.45. Found: C, 74.47; H, 8.22; N, 12.01.

4.4.2 General Procedure for the Condensation of Naphthols, Aldehydes, and Benzotriazole

A mixture of naphthol (7.2 g, 50 mmol), benzotriazole (5.3 g, 50 mmol), the corresponding aldehyde (50 mmol), and piperidine (0.57 g, 6.7 mmol) in toluene (100 ml) was heated under reflux for the appropriate time, with azeotropical removal of water. Then toluene was removed under reduced pressure to give the crude product, which

was purified as described below. Reaction time, yields, and melting points of the products are given in Table 4.2.

1-(Benzotriazol-1-ylmethyl)-2-naphthol (4.11g). It was prepared from 2-naphthol, paraformaldehyde, and benzotriazole in a yield of 91%. It is identical in all aspects with the sample prepared earlier.

Reaction of 2-naphthol with benzaldehyde and benzotriazole. The crude product was triturated with diethyl ether to give the 1-isomer 4.15a as microcrystals; the residue was chromatographed from petroleum ether (38-56 °C)/EtOAc, 10:1, v/v, to give the 2-isomer 4.16a as microcrystals. With a reaction time of 24 h, 4.15a and 4.16a were obtained in yield of 38% and 51%, respectively. With a reaction time of 2 h, 4.15a and 4.16a were obtained in a yield of 71% and 20%, respectively.

1-[α -(Benzotriazol-1-yl)benzyl]-2-naphthol (4.15a). ^1H NMR (CDCl_3 + DMSO-d_6) δ 7.1-7.4 (m, 10 H), 7.53 (d, J = 7.9 Hz, 1 H), 7.72 (t, J = 8.6 Hz, 2 H), 7.97 (d, J = 7.7 Hz, 1 H), 8.05 (dd, J = 7.4, 2.2 Hz, 1 H), 8.31 (s, 1 H, R_3CH), 10.2 (s, 1 H, OH); ^{13}C NMR (CDCl_3 + DMSO-d_6) δ 57.9, 110.5, 114.1, 117.8, 118.8, 122.2, 123.4, 124.1, 125.8, 126.5, 127.1, 127.5, 127.9, 128.1, 128.5, 130.5, 132.2, 133.6, 137.3, 144.8, 153.7.

Anal. Calcd for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.40; H, 4.83; N, 11.90.

1-[α -(Benzotriazol-2-yl)benzyl]-2-naphthol (4.16a).

^1H NMR δ 6.75-6.85 (m, 2 H), 7.15-7.40 (m, 7 H), 7.57 (dt, $J = 7.2, 1.5$ Hz, 1 H), 7.8-7.9 (m, 4 H), 8.35 (d, $J = 9.6$ Hz, 1 H), 8.36 (s, 1 H, R_3CH), 10.20 (s, 1 H, OH); ^{13}C NMR δ 66.6, 115.3, 118.0, 121.0, 121.6, 123.5, 126.0, 127.3, 127.7, 128.0, 128.6, 129.0, 129.2, 131.9, 133.2, 137.4, 143.5, 154.8.

Anal. Calcd for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.40; H, 4.77; N, 11.90.

Reaction of 2-naphthol with 4-dimethylaminobenzaldehyde and benzotriazole. The crude product was triturated with diethyl ether to give a solid, which was then recrystallized from EtOAc to give the 1-isomer 4.15b as microcrystals. The residues from the trituration and the recrystallization were chromatographed from methylene chloride to give the 2-isomer 4.16b (23%) as microcrystals and additional 1-isomer 4.15b. The 1-isomer 4.15b was obtained in a total yield of 63%.

1-[1-(Benzotriazol-1-yl)-1-(4-dimethylaminophenyl)]-methyl-2-naphthol (4.15b). ^1H NMR ($CDCl_3 + DMSO-d_6$) δ 2.91 (s, 6 H), 6.63 (d, $J = 8.8$ Hz, 2 H), 7.10 (d, $J = 8.6$ Hz,

2 H), 7.16–7.38 (m, 6 H), 7.68 (d, $J = 8.8$ Hz, 2 H), 7.91–7.97 (m, 1 H), 8.07 (d, $J = 7.9$ Hz, 1 H), 8.17 (s, 1 H, R_3CH), 9.75 (s, 1 H, OH); ^{13}C NMR ($CDCl_3 + DMSO-d_6$) δ 39.3, 58.1, 110.4, 111.1, 114.3, 117.4, 118.1, 121.6, 122.5, 123.0, 123.1, 125.3, 125.6, 127.5, 127.9, 128.5, 129.5, 131.7, 133.1, 144.4, 148.9, 152.7.

Anal. Calcd for $C_{25}H_{22}N_4O$: C, 76.12; H, 5.62; N, 14.20. Found: C, 76.17; H, 5.63; N, 14.02.

1-[1-(Benzotriazol-2-yl)-1-(4-dimethylaminophenyl)]-methyl-2-naphthol (4.16b). ^1H NMR δ 2.82 (s, 6 H), 6.54 (d, $J = 8.8$ Hz, 2 H), 6.76 (d, $J = 8.9$ Hz, 2 H), 7.25–7.40 (m, 4 H), 7.53 (t, $J = 8.3$ Hz, 1 H), 7.76–7.90 (m, 4 H), 8.32 (d, $J = 6.4$ Hz, 1 H), 8.33 (s, 1 H, R_3CH), 10.22 (s, 1 H, OH); ^{13}C NMR δ 40.2, 66.6, 112.1, 114.8, 117.9, 121.1, 121.4, 123.3, 123.9, 127.0, 127.3, 127.4, 128.9, 129.1, 131.5, 133.1, 143.4, 150.1, 154.9.

Anal. Calcd for $C_{25}H_{22}N_4O$: C, 76.12; H, 5.62; N, 14.20. Found: C, 76.00; H, 5.67; N, 14.03.

Reaction of 2-naphthol with 1-heptaldehyde and benzotriazole. The crude product was triturated with diethyl ether/hexane to give a solid, which was washed with 2.5% of NaOH solution to give the 1-isomer 4.15c (10%) as needles. Acidification of the NaOH solution gave recovered 2-naphthol in 52% yield. The residue from the

trituration was chromatographed from petroleum ether (38-56 °C)/EtOAc, 10:1, v/v, to give the 2-isomer **4.16c** (15%) as plates.

1-[1-(Benzotriazol-1-yl)heptyl]-2-naphthol (**4.15c**).

^1H NMR (CDCl_3 + DMSO-d_6) δ 0.83 (t, J = 6.8 Hz, 3 H), 1.2-1.6 (m, 7 H), 2.7-3.0 (m, 2 H), 3.2-3.3 (m, 1 H), 6.85 (t, J = 7.1 Hz, 1 H, R_3CH), 7.15-7.40 (m, 5 H), 7.51-7.54 (m, 1 H), 7.66 (t, J = 6.1 Hz, 2 H), 7.93-7.96 (m, 1 H), 8.25 (d, J = 8.4 Hz, 1 H), 9.73 (s, 1 H, OH); ^{13}C NMR (CDCl_3 + DMSO-d_6) δ 13.7, 22.2, 26.6, 28.8, 31.3, 32.0, 56.2, 110.6, 115.3, 118.0, 118.9, 122.4, 122.5, 123.5, 126.3, 126.4, 128.5, 128.9, 130.1, 132.3, 133.3, 145.5, 153.0.

Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}$: C, 76.85; H, 7.01; N, 11.69. Found: C, 77.02; H, 7.24; N, 11.84.

1-[1-(Benzotriazol-2-yl)heptyl]-2-naphthol (**4.16c**).

^1H NMR (CDCl_3 + DMSO-d_6) δ 0.82 (t, J = 6.8 Hz, 3 H), 1.1-1.5 (m, 7 H), 2.6-2.8 (m, 1 H), 3.1-3.4 (m, 2 H), 6.96 (t, J = 8.0 Hz, 1 H, R_3CH), 7.2-7.4 (m, 4 H), 7.69 (t, J = 9.0 Hz, 2 H), 7.82 (q, J = 3.0 Hz, 2 H), 7.96 (d, J = 8.7 Hz, 1 H), 9.80 (broad, 1 H, OH); ^{13}C NMR (CDCl_3 + DMSO-d_6) δ 13.6, 22.0, 26.2, 28.6, 31.1, 32.1, 63.0, 116.1, 117.6, 118.6, 121.9, 122.2, 125.7, 126.2, 128.4, 128.5, 129.8, 132.2, 143.1, 153.4.

Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}$: C, 76.85; H, 7.01; N, 11.69. Found: C, 77.24; H, 7.16; N, 11.79.

Reaction of 1-naphthol with benzaldehyde and benzotriazole. The crude product was chromatographed from hexane/methylene chloride, 1:1, v/v, to give the 1-isomer 4.17 (34%) as microcrystals and the 2-isomer 4.18 (23%) as microcrystals.

2-[α -(Benzotriazol-1-yl)benzyl]-1-naphthol (4.17). ^1H NMR δ 7.0-7.4 (m, 12 H), 7.66-7.72 (m, 2 H), 7.74 (s, 1 H, R_3CH), 8.25-8.31 (m, 1 H), 8.90 (broad, 1 H, OH); ^{13}C NMR δ 62.5, 110.0, 118.8, 119.5, 120.5, 122.1, 124.4, 125.6, 125.7, 126.7, 127.0, 127.3, 127.6, 127.7, 128.0, 128.6, 133.4, 134.6, 137.5, 145.0, 150.6.

Anal. Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.46; H, 4.88; N, 11.65.

2-[α -(Benzotriazol-2-yl)benzyl]-1-naphthol (4.18). ^1H NMR δ 6.85-6.95 (m, 2 H), 7.1-7.4 (m, 9 H), 7.50 (s, 1 H, R_3CH), 7.65-7.85 (m, 3 H), 8.4-8.5 (m, 1 H), 10.4 (s, 1 H, OH); ^{13}C NMR δ 73.9, 116.6, 117.8, 120.1, 123.0, 125.4, 126.4, 126.7, 127.0, 127.1, 127.2, 128.1, 128.4, 128.8, 135.1, 137.1, 143.4, 151.9.

Anal. Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.68; H, 4.89; N, 11.73.

2-(Benzotriazol-1-ylmethyl)-4-methylanisole (4.19).
To a solution of 2-(benzotriazol-1-ylmethyl)-4-methyl-

phenol (4.11c) (2.39 g, 10 mmol) in 1,2-dimethoxyethane (50 ml) at $-78\text{ }^{\circ}\text{C}$ was added *n*-BuLi (2.5 M in hexane; 8.0 ml, 20 mmol). The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, then at room temperature for 2 h, cooled again to $-78\text{ }^{\circ}\text{C}$, and then methyl iodide (0.62 ml, 10 mmol) was added. After allowing to reach room temperature overnight, water (30 ml) was added, the mixture acidified with 2 N HCl, extracted with diethyl ether (3 $\times$ 50 ml), and the organic extracts dried (MgSO_4). The solvent was removed in vacuo, the residue chromatographed from hexane/EtOAc, 2:1, to give unreacted 4.11c (0.57 g, 24%) and compound 4.19 (0.72 g, 28%) as plates (recrystallized from hexane/benzene), m.p. $97\text{--}99\text{ }^{\circ}\text{C}$. ^1H NMR (DMSO-d_6) δ 2.16 (s, 3 H), 3.76 (s, 3 H), 5.86 (s, 2 H), 6.90–7.12 (m, 3 H), 7.38 (t, $J = 8.0\text{ Hz}$, 1 H), 7.52 (t, $J = 8.0\text{ Hz}$, 1 H), 7.78 (d, $J = 8.0\text{ Hz}$, 1 H), 8.06 (d, $J = 8.0\text{ Hz}$, 1 H); ^{13}C NMR (DMSO-d_6) δ 19.9, 46.3, 55.4, 110.7, 111.1, 119.0, 123.1, 123.8, 127.1, 129.2, 130.0, 132.8, 145.1, 154.8.

Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.48; H, 6.04; N, 16.70.

2-(Benzotriazol-1-ylmethyl)-6-methylphenyl acetate (4.20). A solution of 4.11b (1.20 g, 5 mmol) in acetic anhydride (20 ml) was heated under reflux for 30 min, then poured into ice-water (100 ml). The resulted solution was

heated at 100 °C for 30 min. After cooling, the solution was rendered basic with NaOH solution (50%; 30 ml), extracted with chloroform, and the organic extracts dried (MgSO₄). The solvent was removed in vacuo, the residue chromatographed from hexane/EtOAc, 1:1, v/v, to give 4.20 (1.30 g, 92%) as microcrystals, m.p. 74–76 °C. ¹H NMR δ 2.09 (s, 3 H), 2.31 (s, 3 H), 5.70 (s, 2 H), 7.0–7.4 (m, 6 H), 7.98 (d, J = 8.0 Hz, 1 H); ¹³C NMR δ 15.9, 20.2, 47.8, 109.6, 119.5, 123.6, 126.0, 126.6, 126.8, 127.1, 131.2, 131.3, 132.4, 145.9, 147.5, 168.3.

Anal. Calcd for C₁₆H₁₅N₃O₂: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.28; H, 5.31; N, 15.04.

4.4.3 General Procedure for the Lithiation of Compound 4.11

To a solution of the substrate 4.11 (5 mmol) in THF (30 ml) at -78 °C was added *n*-BuLi (2.5 M in hexane; 2.0 ml, 5 mmol). The solution was stirred at -78 °C for 1 h, then trimethylsilyl chloride (0.63 ml, 5 mmol) was added. After stirring at -78 °C for 30 min, and at 25 °C for 30 min, the solution was recooled to -78 °C and *n*-BuLi (2.5 M in hexane; 2.0 ml, 5 mmol) was added. Stirring was continued for 2 h at this temperature and the corresponding electrophile (5 mmol) were added. After allowing to reach room temperature overnight, the solution was

concentrated by removing the solvent in vacuo, then ethanol (95%; 15 ml) and concentrated hydrochloric acid (0.4 ml) was added. After stirring at room temperature for 30 min, ethanol was removed in vacuo, water (30 ml) added, the mixture extracted with diethyl ether (3 × 40 ml), and the organic extracts dried (MgSO₄). The solvent was removed in vacuo and the residue purified as described below.

Physical data of the products, substrates, electrophiles, and yields are given in Table 4.3.

2-(Benzotriazol-1-yl)-2-(2-hydroxyphenyl)-1-phenyl-ethanol (4.21a). Obtained as plates (column chromatography from hexane/EtOAc, 8:1, v/v, followed by recrystallization from methanol). ¹H NMR (CDCl₃ + DMSO-d₆) δ 2.76 (s, 1 H), 4.84 (d, J = 5.2 Hz, 1 H), 6.02 (dd, J = 5.3, 2.6 Hz, 1 H), 6.53 (d, J = 8.1 Hz, 1 H), 6.65-6.80 (m, 2 H), 6.9-7.5 (m, 8 H), 7.62 (d, J = 7.7 Hz, 1 H), 7.95 (d, J = 7.9 Hz, 1 H), 9.13 (s, 1 H); ¹³C NMR (CDCl₃ + DMSO-d₆) δ 61.9, 74.8, 110.3, 115.3, 118.9, 119.1, 122.5, 123.7, 126.8, 127.2, 127.5, 128.5, 128.9, 133.6, 140.3, 144.9, 154.1.

Anal. Calcd for C₂₀H₁₇N₃O₂: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.48; H, 5.14; N, 12.35.

2-[1-(Benzotriazol-1-yl)ethyl]-6-methylphenol (4.21b). Obtained as prisms (recrystallized from

methanol). ^1H NMR δ 2.12 (d, $J = 7.0$ Hz, 3 H), 2.27 (s, 3 H), 6.51 (q, $J = 7.0$ Hz, 1 H, R_3CH), 6.74 (t, $J = 7.6$ Hz, 1 H), 7.01 (t, $J = 6.8$ Hz, 2 H), 7.3–7.5 (m, 3 H), 7.95–8.05 (m, 2 H); ^{13}C NMR δ 16.4, 19.9, 53.0, 110.2, 119.0, 119.8, 123.4, 124.2, 124.7, 126.5, 126.8, 130.3, 132.4, 145.5, 151.8.

Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}$: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.77; H, 6.05; N, 16.45.

2-[1-(Benzotriazol-1-yl)pentyl]-6-methylphenol

(4.21c). Obtained as plates (column chromatography from petroleum ether (38–56 °C)/EtOAc, 8:1, v/v). ^1H NMR δ 0.83 (t, $J = 6.9$ Hz, 3 H), 1.2–1.4 (m, 4 H), 2.29 (s, 3 H), 2.40–2.55 (m, 1 H), 2.7–2.8 (m, 1 H), 6.16 (dd, $J = 8.8$, 6.6 Hz, 1 H), 6.78 (t, $J = 7.6$ Hz, 1 H, R_3CH), 7.06 (d, $J = 7.4$ Hz, 1 H), 7.20 (dd, $J = 7.8$, 1.3 Hz, 1 H), 7.30 (dt, $J = 7.0$, 1.1 Hz, 1 H), 7.39 (dt, $J = 7.0$, 1.1 Hz, 1 H), 7.52 (s, 1 H), 7.63 (d, $J = 8.3$ Hz, 1 H), 7.98 (d, $J = 8.3$ Hz, 1 H); ^{13}C NMR δ 13.8, 16.3, 22.2, 28.8, 33.6, 59.1, 110.0, 119.6, 120.4, 124.1, 125.4, 126.1, 127.3, 130.9, 133.1, 145.4, 152.2.

Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.10; H, 7.31; N, 14.16.

2-(Benzotriazol-1-yl)-2-(2-hydroxy-3-methylphenyl)-acetic acid (4.21d). Obtained as microcrystals (recrystal-

lized from EtOH/EtOAc). ^1H NMR (DMSO- d_6) δ 2.20 (s, 3 H), 4.70 (broad, 1-2 H), 6.87 (t, J = 7.6 Hz, 1 H), 7.15 (d, J = 7.4 Hz, 1 H), 7.18 (s, 1 H, R_3CH), 7.26 (d, J = 6.7 Hz, 1 H), 7.34 (t, J = 7.1 Hz, 1 H), 7.42 (t, J = 7.0 Hz, 1 H), 7.54 (d, J = 8.3 Hz, 1 H), 8.00 (d, J = 8.3 Hz, 1 H); ^{13}C NMR (DMSO- d_6) δ 16.9, 60.6, 111.2, 119.3, 119.7, 121.2, 124.0, 125.6, 127.4, 127.5, 132.0, 133.1, 145.4, 153.7, 169.9.

Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.31; H, 4.70; N, 14.52.

2-(Benzotriazol-1-yl)-2-(2-hydroxy-3-methylphenyl)-1,1-diphenylethanol (4.21e). Obtained as microcrystals (recrystallized from toluene). ^1H NMR (DMSO- d_6) δ 1.74 (s, 3 H), 3.11 (s, 1 H), 6.30 (t, J = 7.6 Hz, 1 H), 6.46 (s, 1 H, R_3CH), 6.58 (d, J = 6.7 Hz, 1 H), 6.7-7.0 (m, 8 H), 7.08 (t, J = 7.1 Hz, 1 H), 7.22 (s, 1 H), 7.31 (d, J = 7.6 Hz, 2 H), 7.50 (d, J = 8.3 Hz, 1 H), 7.58 (d, J = 8.3 Hz, 1 H), 7.63 (d, J = 7.8 Hz, 1 H), 8.70 (s, 1 H, OH); ^{13}C NMR (DMSO- d_6) δ 16.8, 62.8, 81.3, 112.0, 118.7, 118.8, 123.3, 123.5, 124.5, 125.6, 126.2, 126.6, 126.7, 127.6, 127.7, 129.6, 130.5, 133.4, 144.3, 144.5, 145.7, 153.3.

Anal. Calcd for $\text{C}_{27}\text{H}_{23}\text{N}_3\text{O}_2$: C, 76.94; H, 5.50; N, 9.97. Found: C, 76.97; H, 5.58; N, 9.97.

2-[Bis(phenylthio)methyl]-6-methylphenol (4.22). Obtained as an oil (column chromatography from

hexane/EtOAc, 30:1, v/v). ^1H NMR δ 2.21 (s, 3 H), 5.72 (s, 1 H), 6.47 (s, 1 H), 6.64 (t, J = 7.6 Hz, 1 H), 6.98 (dd, J = 7.4, 2.5 Hz, 2 H), 7.16–7.21 (m, 6 H), 7.34–7.38 (m, 4 H); ^{13}C NMR δ 15.9, 57.1, 120.0, 123.4, 125.4, 127.1, 127.9, 128.8, 130.9, 132.4, 133.6, 152.1.

Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{OS}_2$: C, 70.97; H, 5.36. Found: C, 71.02; H, 5.38.

4.4.4 General Procedure for the Displacement of Benzotriazole

4.4.4.1 By lithium aluminum hydride

To a solution of the corresponding benzotriazole adduct (1.0 mmol) in THF (15 ml) [toluene (15 ml) was used as the solvent for 4.11b] was added lithium aluminum hydride (0.12 g, 2.5 mmol). The resulted solution was heated under reflux for the appropriate time, cooled, and poured into ice-water (20 ml), acidified with 2 N HCl. The mixture extracted with diethyl ether (3 $\times$ 30 ml) and the organic extracts dried (MgSO_4). The solvent was removed in vacuo, the residue purified.

Physical data of the products, substrates, reagents, reaction time, yields, and purification solvents are given in Table 4.4. Further purification for the analytically pure sample is described for the particular compound.

2-Methyl-6-pentylphenol (4.23b). Obtained as an oil. ^1H NMR δ 0.89 (t, J = 6.9 Hz, 3 H), 1.3–1.4 (m, 4 H),

1.55-1.65 (m, 2 H), 2.22 (s, 3 H), 2.58 (t, $J = 6.9$ Hz, 2 H), 6.76 (t, $J = 7.4$ Hz, 1 H), 6.95 (d, $J = 7.4$ Hz, 2 H); ^{13}C NMR δ 14.0, 15.8, 22.5, 29.4, 30.0, 31.7, 120.2, 123.0, 127.7, 127.9, 128.4, 151.7.

Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}$: C, 80.85; H, 10.18. Found: C, 81.04; H, 10.23.

2,6-Dimethylphenol (4.23c). Obtained as plates. ^1H NMR δ 2.20 (s, 6 H), 4.69 (s, 1 H), 6.73 (t, $J = 7.6$ Hz, 1 H), 6.94 (d, $J = 7.6$ Hz, 2 H); ^{13}C NMR δ 15.7, 120.2, 123.0, 128.5, 152.1.

2-Ethyl-6-methylphenol (4.24c). Obtained as an oil. ^1H NMR δ 1.22 (t, $J = 7.6$ Hz, 3 H), 2.23 (s, 3 H), 2.61 (q, $J = 7.6$ Hz, 2 H), 4.64 (broad, 1 H), 6.78 (t, $J = 7.3$ Hz, 1 H), 6.97 (t, $J = 6.8$ Hz, 2 H); ^{13}C NMR δ 14.0, 15.8, 23.0, 120.3, 123.0, 126.8, 128.4, 129.2, 151.6.

1-Benzyl-2-naphthol (4.25a). Obtained as plates (recrystallized from hexane/benzene). ^1H NMR δ 4.40 (s, 2 H), 5.09 (s, 1 H), 7.00 (d, $J = 8.8$ Hz, 1 H), 7.1-7.2 (m, 5 H), 7.28 (t, $J = 6.9$ Hz, 1 H), 7.39 (t, $J = 7.5$ Hz, 1 H), 7.62 (d, $J = 8.8$ Hz, 1 H), 7.74 (d, $J = 5.1$ Hz, 1 H), 7.86 (d, $J = 8.6$ Hz, 1 H); ^{13}C NMR δ 30.6, 117.8, 118.1, 123.2, 123.3, 126.1, 126.6, 128.1, 128.4, 128.48, 128.51, 129.4, 133.6, 140.0, 151.1.

1-(4-Dimethylaminophenyl)methyl-2-naphthol (4.25b).

Obtained as microcrystals. ^1H NMR δ 2.84 (s, 6 H), 4.33 (s, 2 H), 5.25 (s, 1 H), 6.63 (d, $J = 8.8$ Hz, 2 H), 7.04 (d $J = 3.7$ Hz, 1 H), 7.07 (d, $J = 3.7$ Hz, 2 H), 7.30 (dt, $J = 8.0, 1.1$ Hz, 1 H), 7.42 (dt, $J = 8.0, 1.1$ Hz, 1 H), 7.64 (d, $J = 8.6$ Hz, 1 H), 7.76 (d, $J = 8.1$ Hz, 1 H), 7.94 (d, $J = 8.5$ Hz, 1 H); ^{13}C NMR δ 29.7, 40.9, 113.3, 118.0, 118.7, 123.0, 123.3, 126.5, 127.7, 128.2, 128.4, 128.8, 129.4, 133.6, 149.3, 151.4.

4.4.4.2 By Grignard reagents

To a solution of the appropriate benzotriazole adduct (2 mmol) in THF (20 ml) [toluene (20 ml) was used as the solvent for 4.11b] at room temperature (or at -78 °C for 4.15b) was added the corresponding Grignard reagent (12 mmol) in diethyl ether. The reaction mixture was stirred at room temperature (for 4.15a,b) or heated under reflux (for 4.11b, diethyl ether was distilled off until the temperature reached the boiling point of toluene) for the appropriate time until TLC indicated the starting material had been consumed. The reaction mixture was then poured into ice-water (20 ml), acidified with 2 N HCl, the mixture extracted with diethyl ether (3×30 ml), and the organic extracts dried (MgSO_4). The solvent was removed in vacuo and the residue purified.

Physical data of the products, substrates, reagents, reaction time, yields, and purification solvents are given in Table 4.4. Further purification for the analytically pure sample is described for the particular compound.

2-Benzyl-6-methylphenol (4.23a). Obtained as an oil. ^1H NMR δ 2.19 (s, 3 H), 3.96 (s, 2 H), 4.60 (s, 1 H), 6.75–6.82 (m, 1 H), 6.95–7.05 (m, 2 H), 7.1–7.3 (m, 5 H); ^{13}C NMR δ 15.8, 36.6, 120.4, 123.8, 126.4, 128.6, 128.7, 129.3, 129.4, 139.8, 142.5, 152.1.

2-Methyl-6-pentylphenol (4.23b). It was obtained from the reaction of 4.11b with *n*-BuMgBr in 29% yield. It is identical in all aspects with the sample prepared earlier.

2-(α -Methylbenzyl)-6-methylphenol (4.24a). Obtained as an oil. ^1H NMR δ 1.59 (d, $J = 7.2$ Hz, 3 H), 2.13 (s, 3 H), 4.30 (q, $J = 7.2$ Hz, 1 H), 4.59 (s, 1 H), 6.83 (t, $J = 7.6$ Hz, 1 H), 6.98 (dd, $J = 7.4, 0.8$ Hz, 1 H), 7.1–7.3 (m, 6 H); ^{13}C NMR δ 15.8, 21.2, 39.0, 120.3, 124.0, 125.5, 126.4, 127.4, 128.7, 128.9, 131.3, 145.3, 151.6.

2-(1-Benzylethyl)-6-methylphenol (4.24b). Obtained as an oil. ^1H NMR δ 1.99 (d, $J = 7.2$ Hz, 3 H), 2.17 (s, 3 H), 2.71 (dd, $J = 13.3, 8.5$ Hz, 1 H), 2.96 (dd, $J = 13.3, 5.9$ Hz, 1 H), 3.34 (sext, $J = 8.1$ Hz, 1 H), 4.52 (broad, 1 H),

6.81 (t, $J = 7.6$ Hz, 1 H), 6.9–7.4 (m, 7 H); ^{13}C NMR δ 15.9, 19.7, 34.6, 43.7, 120.4, 123.0, 124.7, 125.8, 128.1, 128.2, 129.1, 132.5, 141.0, 151.2. MS (HR) for $\text{C}_{16}\text{H}_{18}\text{O}$ Calcd: 226.1344. Found: 226.1347.

1-Diphenylmethyl-2-naphthol (4.25c). Obtained as prisms (recrystallized from hexane/EtOAc). ^1H NMR δ 5.18 (s, 1 H), 6.41 (s, 1 H), 7.05 (d, $J = 8.8$ Hz, 1 H), 7.2–7.5 (m, 11 H), 7.72 (d, $J = 8.9$ Hz, 1 H), 7.77 (d, $J = 8.1$ Hz, 1 H), 7.97 (d, $J = 8.6$ Hz, 1 H); ^{13}C NMR δ 48.6, 119.8, 120.1, 122.8, 123.2, 126.8, 127.2, 128.7, 129.0, 129.1, 129.6, 129.7, 133.4, 141.6, 152.8.

1-(α -Benzylbenzyl)-2-naphthol (4.25d). Obtained as an oil. ^1H NMR δ 3.54 (dd, $J = 13.4, 9.1$ Hz, 1 H), 3.76 (dd, $J = 13.4, 6.4$ Hz, 1 H), 4.92 (s, 1 H), 5.33 (dd, $J = 8.7, 7.4$ Hz, 1 H), 6.87 (d, $J = 8.8$ Hz, 1 H), 6.95–7.05 (m, 4 H), 7.1–7.3 (m, 6 H), 7.39 (d, $J = 7.2$ Hz, 2 H), 7.56 (d, $J = 8.6$ Hz, 1 H), 7.67 (dd, $J = 7.8, 1.5$ Hz, 1 H), 7.84 (d, $J = 8.1$ Hz, 1 H); ^{13}C NMR δ 37.7, 42.5, 118.8, 122.2, 122.9, 123.2, 125.8, 126.2, 126.4, 127.6, 127.9, 128.6, 128.7, 128.8, 129.0, 129.5, 133.3, 140.3, 143.3, 151.6. MS (HR) for $\text{C}_{24}\text{H}_{20}\text{O}$ Calcd: 324.1508. Found: 324.1510.

1-[α -(4-Dimethylaminophenyl)benzyl]-2-naphthol (4.25e). Obtained as plates (recrystallized from

hexane/EtOAc). ^1H NMR δ 2.88 (s, 6 H), 6.39 (s, 1 H), 6.64 (d, J = 8.8 Hz, 2 H), 7.1–7.3 (m, 11 H), 7.65 (d, J = 8.8 Hz, 1 H), 7.72 (dd, J = 7.8, 1.0 Hz, 1 H), 7.90 (d, J = 8.6 Hz, 1 H); ^{13}C NMR δ 40.3, 46.7, 112.5, 119.2, 120.8, 122.3, 123.6, 125.8, 125.9, 128.1, 128.3, 128.6, 128.8, 129.1, 129.5, 133.3, 143.1, 149.0, 152.8.

Anal. Calcd for $\text{C}_{25}\text{H}_{23}\text{NO}$: C, 84.95; H, 6.56; N, 3.96.
Found: C, 84.77; H, 6.65; N, 3.65.

1-[1-Benzyl-1-(4-dimethylaminophenyl)]methyl-2-naphthol (4.25f). Obtained as microcrystals. ^1H NMR δ 2.85 (s, 6 H), 3.42 (dd, J = 13.9, 8.8 Hz, 1 H), 3.70 (dd, J = 13.7, 6.8 Hz, 1 H), 5.27 (t, J = 7.8 Hz, 1 H), 5.36 (broad, 1 H), 6.64 (d, J = 8.8 Hz, 2 H), 6.9–7.3 (m, 10 H), 7.57 (d, J = 8.8 Hz, 1 H), 7.67 (dd, J = 7.9, 1.2 Hz, 1 H), 7.85 (d, J = 8.6 Hz, 1 H); ^{13}C NMR δ 37.6, 40.6, 41.2, 113.2, 119.2, 122.5, 122.7, 125.7, 126.0, 127.9, 128.3, 128.4, 128.6, 128.8, 129.3, 133.4, 140.3, 149.3, 152.0.

Anal. Calcd for $\text{C}_{26}\text{H}_{25}\text{NO}$: C, 84.98; H, 6.86; N, 3.81.
Found: C, 84.95; H, 6.90; N, 3.68.

CHAPTER V
N-[α -(o- AND p-METHOXYARYL)ALKYL]BENZOTRIAZOLES:
PREPARATION AND USE IN SYNTHESIS

5.1 Introduction

5.1.1 Importance and Synthesis of Phenol Ethers

Many natural products and synthetic targets possess phenol ether fragments [39JCS89, 52JCS4964, 85CL1687]. For example, compound 5.1 occurs in the essential oils from various species of *Myrthaecae* [39JCS89]. Phenol ethers are also involved in various transformations of organic compounds. Naphthyl vinyl ethers of type 5.2 are used for photocyclization reactions yielding compounds containing dihydrofuran ring systems [80S847]. Such a photocyclization has been shown to be a useful method for synthesizing compounds of medicinal importance [78JA2150].

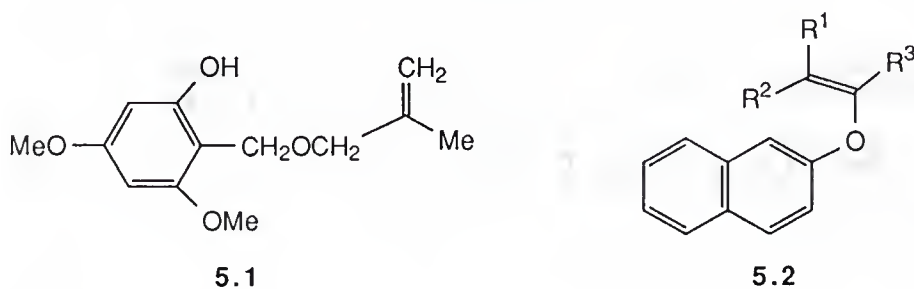


Figure 5.1 Phenol Ethers

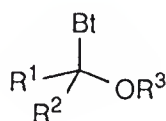
Phenol ethers have long been employed in the fragrance and flavor industries [80MI3]. Reactions between phenol ethers and aldehydes give carbinols or alkoxydiphenylalkanes depending on the reaction conditions used. Such products are precursors for the synthesis of fragrance and flavor substances [80MI3].

A wide variety of procedures have been developed for the preparation of phenol ethers [70MI2]. The commonly used methods involve alkylation of the parent phenol or the phenoxide ion, with the latter being the more important. The reactions involving the alkylation of the phenoxide ion can be carried out in organic solvents or in aqueous media. If organic solvents are used, the phenoxide ion is generated by treatment of the phenol with a base such as sodium, sodium hydride or sodium amide in a solvent such as benzene, toluene or dioxane; alkylation with the appropriate alkyl halide is then normally carried out in the same solvent. This method is usually highly efficient, although some care must be exercised in the choice of solvent in order to avoid formation of both C- and O-alkylated products [60JA4675, 63JA1148]. The alkylation of the phenoxide ion in aqueous media employs a phase-transfer catalyst such as a quaternary ammonium salt; dialkyl sulfate esters or alkyl halides are usually used as the alkylating agents. Generally, excellent yields of the desired ethers are obtained.

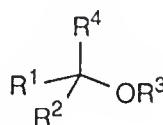
Direct alkylation of the parent phenol which does not require the formation of the phenoxide ion is also used. The alkylating agents used include diazomethane [70MI2], alkyl orthocarbonate esters [56ACS1006], and dialkyl oxalate esters [72JOC3944]. The reactions of phenols with alcohols in the presence of dicyclohexylcarbodiimide for the preparation of phenol ethers have also been reported [66CB1479].

5.1.2 Aim of the Work

The use of benzotriazole as a synthetic auxiliary allows efficient synthesis of a variety of nitrogen containing compounds [89JCS(P1)225 and references therein]. Recently, this work has been extended to the preparation of ethers 5.4 from the alkoxy adducts of type 5.3 [89JOC6022, 90JCS(P1)1717].



5.3



5.4

Figure 5.2 Benzotriazolyl Alkoxy Adducts and Ethers

In Chapters II-IV, we have described the use of benzotriazole in the transformations of anilines and phenols. In Chapter IV, we have demonstrated a convenient synthesis of substituted phenols. One of the differences between the phenol system and the phenol ether system is that in the former case, the phenoxide ion increases the reactivity of the phenol ring which assists the displacement of the benzotriazole group. While such an ion is impossible in the phenol ether system, a lower reactivity is expected. It is thus of interest to examine the reactivity of benzotriazole in a phenol ether system. Activation of an aromatic ring by a methoxy group could assist the electrophilic alkylation with 1-hydroxymethylbenzotriazole to give derivatives. The methylene groups can then be substituted via lithiation. The subsequent displacement of the benzotriazolyl moiety would allow the synthesis of substituted phenol ethers.

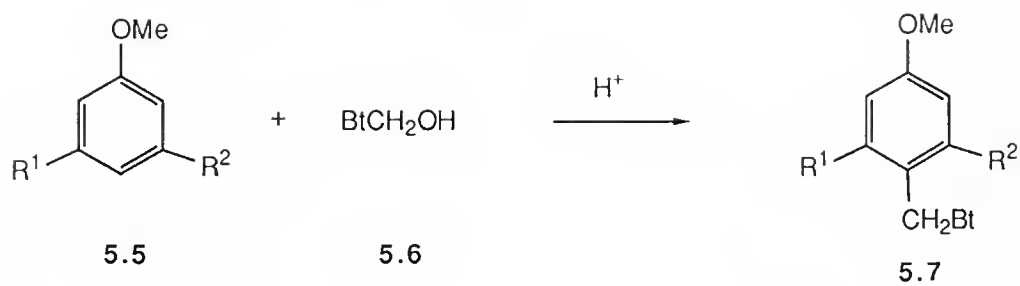
5.2 Results and Discussion

5.2.1 Synthesis of (Benzotriazol-1-ylmethyl)phenyl Methyl Ethers

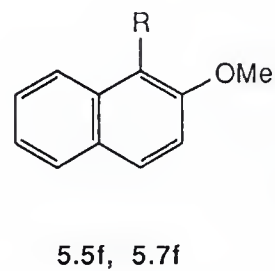
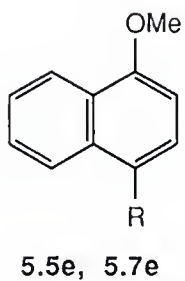
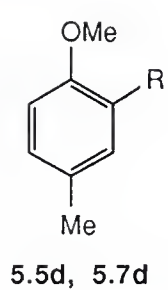
5.2.1.1 By direct alkylation of methoxybenzenes

Anisole and 1,3-dimethoxybenzene, on heating with 1-hydroxymethylbenzotriazole (5.6) in toluene in the

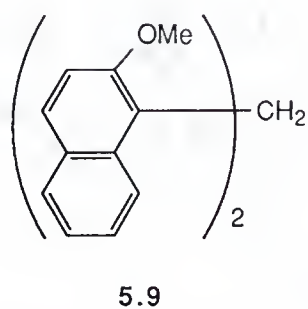
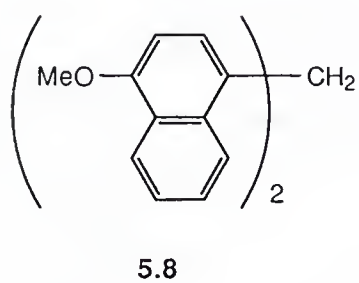
presence of *p*-toluenesulfonic acid, gave the corresponding alkylated products 5.7a and 5.7b, respectively. Reaction of 1,3,5-trimethoxybenzene with 5.6 in refluxing acetic acid gave 5.7c. These alkylations all occur at positions para to a methoxy group. When the para position is occupied, the reaction occurs ortho to the methoxy group as shown in the alkylation of *p*-methylanisole (5.5d) to give 5.7d in a yield of 24%. A similar behavior is found in the benzotriazolylmethylation of 1- and 2-methoxynaphthalenes. In 1-methoxynaphthalene where a para position is available, the alkylation occurs at the 4-position to give 5.7e. While the alkylation of 2-methoxynaphthalene, where a para-position is not available, occurs at the ortho, i.e. the 1-position, to give 5.7f. In the reactions of 1- and 2-methoxynaphthalenes with 5.6, by-products 5.8 and 5.9 are also obtained in yields of 46% and 18%, respectively. Obviously 5.8 and 5.9 are formed by further reactions of 5.7e and 5.7f with more methoxynaphthalene (5.8 and 5.9 have previously been prepared by the direct reaction of the corresponding methoxynaphthalene with formaldehyde [56JOC1310, 59AC(R)1472]). This is confirmed by the formation of 5.9 in 73% yield from the reaction of 5.7f with 2-methoxynaphthalene.



5.5, 5.7	R ¹	R ²
a	H	H
b	H	OMe
c	OMe	OMe



	5.5d-f	5.7d-f
R	H	CH ₂ Bt



Scheme 5.1

5.2.1.2 By conversion of the corresponding phenol to its methyl ether

The preparations of the o-(benzotriazolylmethyl)-phenols 5.11 and 5.19 are described in Chapter IV. Treatment of 5.11 and 5.19 with sodium hydride in DMSO, followed by addition of methyl iodide, afforded the corresponding methyl ethers 5.12 (97%) and 5.7f (90%), respectively (Schemes 5.3 and 5.6).

Table 5.1 Preparation of (Benzotriazol-1-ylmethyl)phenyl Methyl Ethers

Compound	Reaction time, h	Yield ^a (%)	M.p. (°C)	Purification ^b
5.7a	48	30	78-80	7:1
5.7b	25 ^c	37	68-70	4:1
5.7c	48 ^d	52	159-161	ether ^e
5.7d	48	24	97-99	10:1
5.7e	1	30	168-170	10:1
5.7f	5	50 ^f	171-173	10:1
5.12	-	97	64-66	-

^a Isolated yields.

^b Purified by column chromatography. The ratio indicates that of the eluent used, petroleum ether (38-56 °C) to EtOAc, v/v. Further purification for the analytically pure sample is described in the Experimental section.

^c THF was used as the solvent.

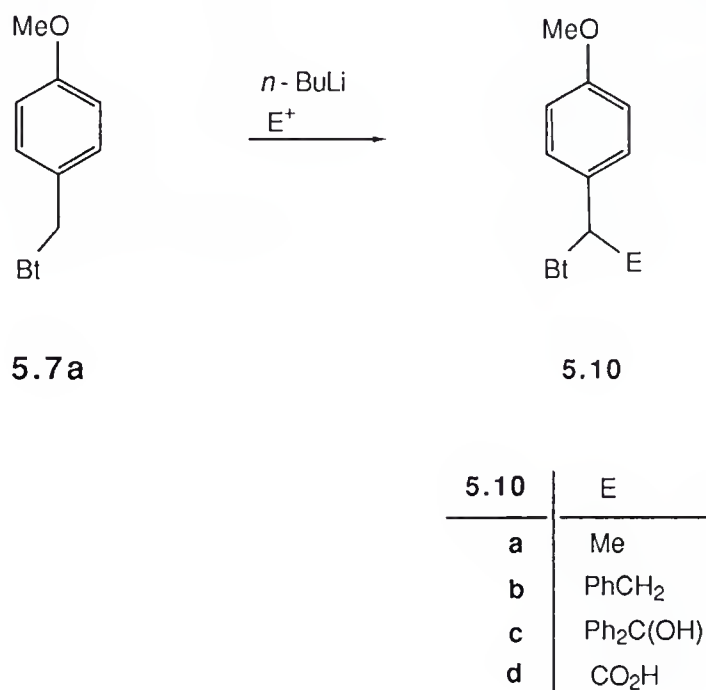
^d Acetic acid was used both as the solvent and as the acid catalyst.

^e Trituration.

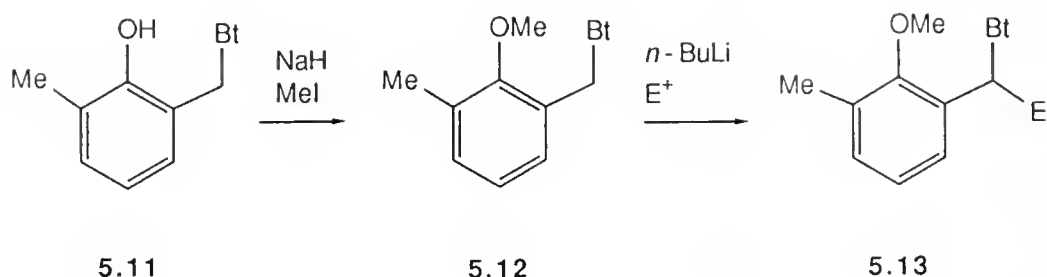
^f Compound 5.7f was also obtained from 5.19 in 90% yield.

5.2.2 Lithiation of (Benzotriazol-1-ylmethyl)phenyl Methyl Ethers

The phenol ether derivatives 5.7 and 5.12 possess relatively acidic methylene groups, which are benzylic and also attached to an electron-withdrawing benzotriazole group. These methylene groups are indeed capable of ready deprotonation. Treatment of the ethers 5.7a and 5.12 with *n*-BuLi, followed by trapping the resulting anions with a variety of electrophiles, gave the expected products 5.10a-d and 5.13a-f, respectively in good yields (see Schemes 5.2, 5.3 and Table 5.2).



Scheme 5.2

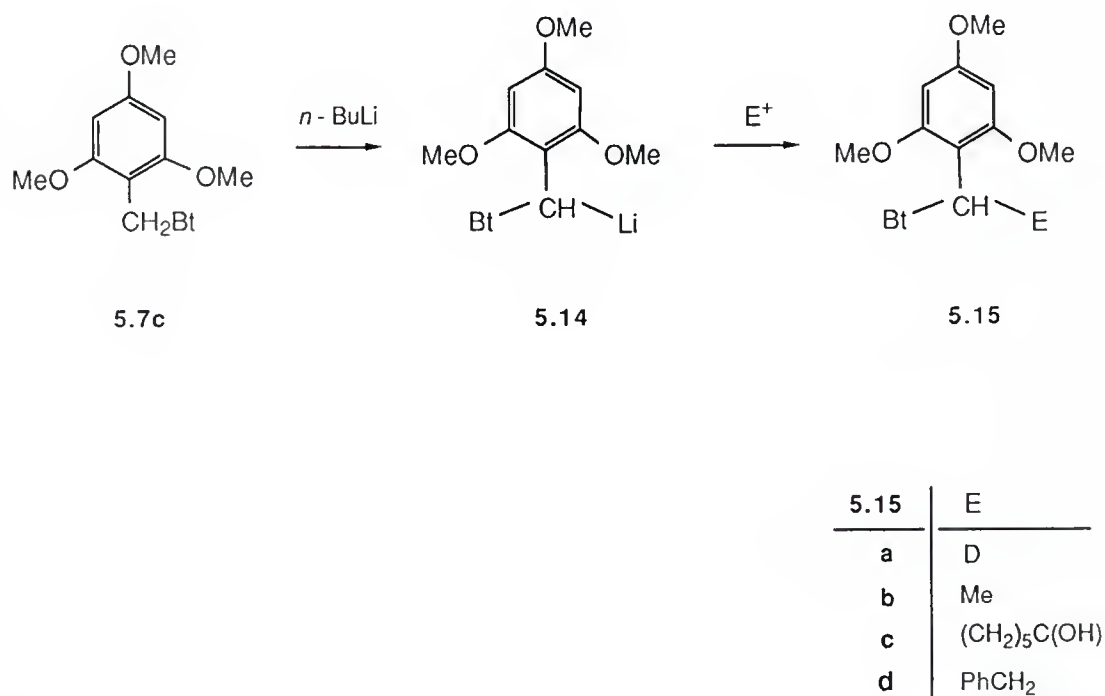


5.13	E
a	Me
b	PhCH ₂
c	<i>p</i> -CH ₃ C ₆ H ₄ CH(OH)
d	(CH ₂) ₅ C(OH)
e	Ph ₂ C(OH)
f	PhC=O

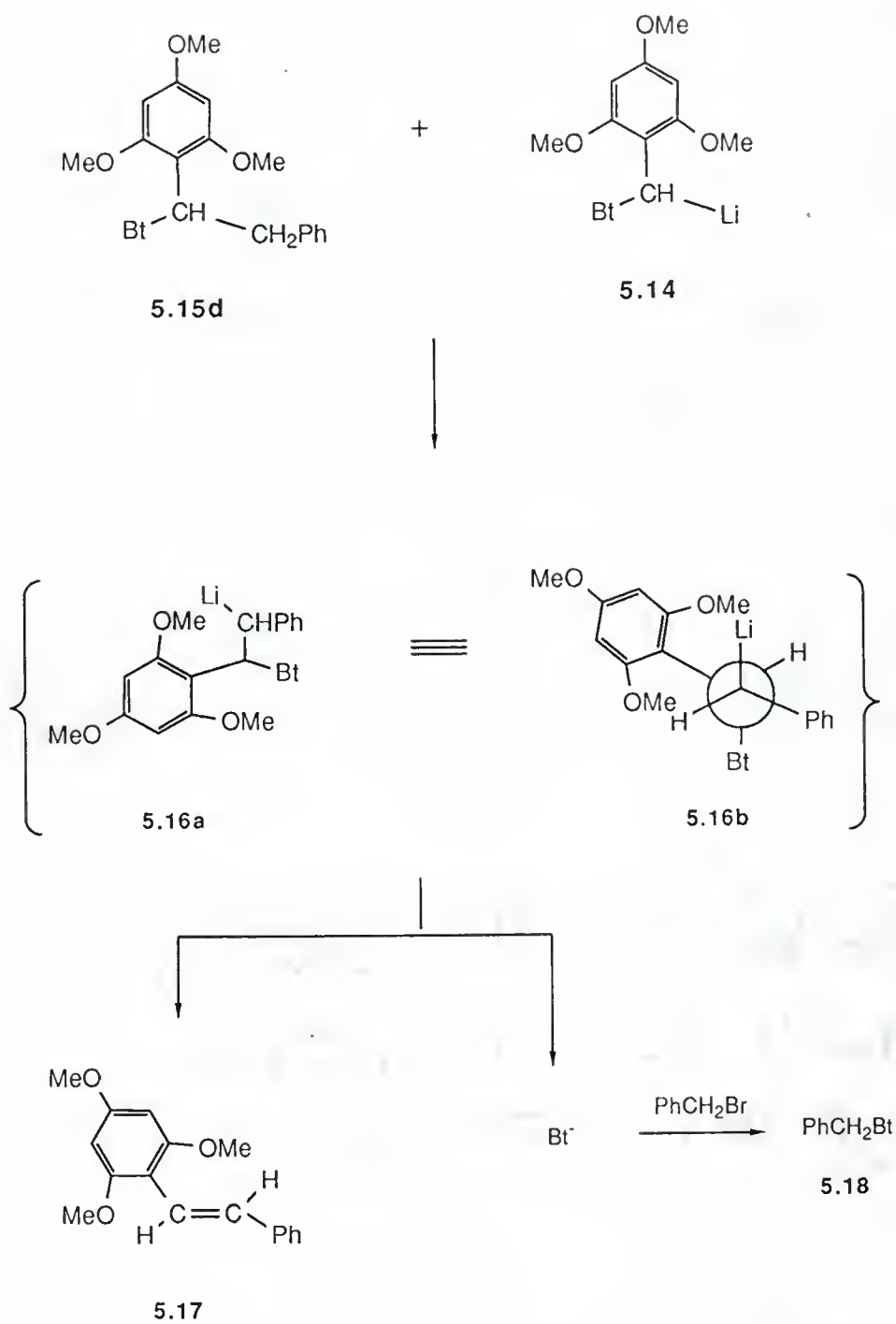
Scheme 5.3

For substrate 5.7c, while attack at the methylene group is more hindered due to the presence of the ortho methoxy substituents, reactions of the anion 5.14 with deuterium oxide, methyl iodide, or cyclohexanone did give the desired products 5.15a-c (Scheme 5.4). However, with benzyl bromide, the desired product 5.15d was accompanied by the formation of trans-1-(2,4,6-trimethoxyphenyl)-2-phenylethene (5.17) and 1-benzylbenzotriazole (5.18). Compound 5.15d may be partially deprotonated by the co-

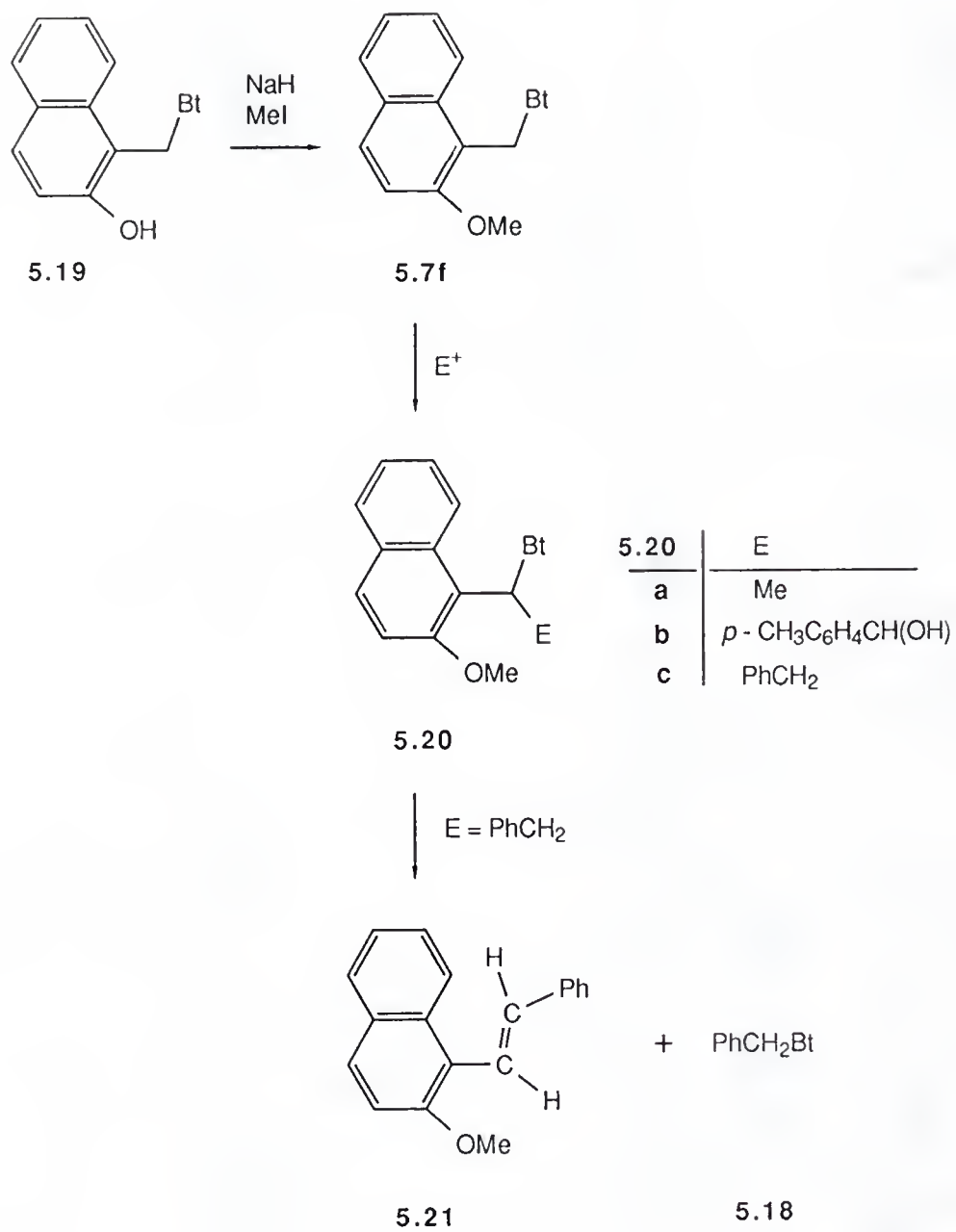
existing lithio salt 5.14 to give 5.16 (the methine proton while more acidic, is more hindered). Anti-elimination of the benzotriazole anion from 5.16 releases the strain energy to give the trans-alkene 5.17. Subsequent attack of the benzotriazole anion on benzyl bromide affords 5.18 (Scheme 5.5). The same phenomenon was observed with substrate 5.7f which reacted with benzyl bromide to give a low yield of the expected product 5.20c along with compounds 5.18 and 5.21 (Scheme 5.6).



Scheme 5.4



Scheme 5.5



Scheme 5.6

Table 5.2 Lithiation of (Benzotriazol-1-ylmethyl)phenyl Methyl Ethers

Substrate	Electrophile	Product	Yield ^a (%)	M.p. (°C)	Purification solvent
5.7a	MeI	5.10a	80	83-85	7:1 ^b
5.7a	PhCH ₂ Br	5.10b	85	134-136	hexane/C ₆ H ₆ ^c
5.7a	Ph ₂ C=O	5.10c	80	200-202	hexane/C ₆ H ₆ ^c
5.7a	CO ₂	5.10d	78	192-194	MeOH/EtOAc ^c
5.12	MeI	5.13a	90	95-97	- ^d
5.12	PhCH ₂ Br	5.13b	70	102-104	8:1 ^b
5.12	PTA ^e	5.13c	87 ^f	200-202	3:1 ^b
5.12	PTA ^e	5.13c	87 ^g	152-154	3:1 ^b
5.12	(CH ₂) ₅ C=O	5.13d	80	147-149	hexane ^h
5.12	Ph ₂ C=O	5.13e	75	195-197	5:1 ^b
5.12	PhCOOEt	5.13f	76	102-104	3:1 ^b
5.7c	D ₂ O	5.15a	95	160-162	- ^d
5.7c	MeI	5.15b	85	117-119	12:1 ^b
5.7c	(CH ₂) ₅ C=O	5.15c	72	116-118	10:1 ^b
5.7c	PhCH ₂ Br	5.15d	64	124-126	10:1 ^b
5.7f	MeI	5.20a	98	131-133	- ^d
5.7f	PTA ^e	5.20b	60	213-215	Et ₂ O ^h
5.7f	PhCH ₂ Br	5.20c	16	124-126	CH ₂ Cl ₂ ^b

^a Isolated yields.

^b Purified by column chromatography. The ratio indicates that of eluent, petroleum ether (38-56 °C)/EtOAc, v/v. Further purification for the analytically pure sample is described in the Experimental section.

^c Purified by recrystallization.

^d The product obtained after work-up is essentially pure.

^e p-Tolualdehyde.

^f Isomer I (The isolated yield of pure isomer I is 25%).

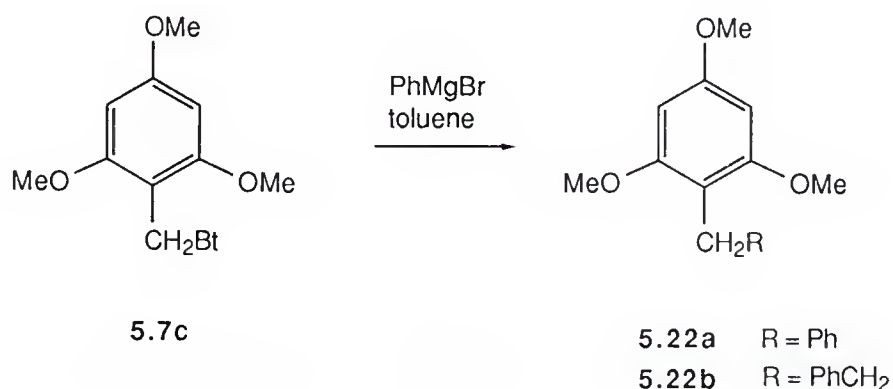
^g Isomer II (The isolated yield of pure isomer II is 36%).

^h The crude product was triturated with the solvent indicated.

5.2.3 Displacement of the Benzotriazole Group

5.2.3.1 By Grignard Reagents

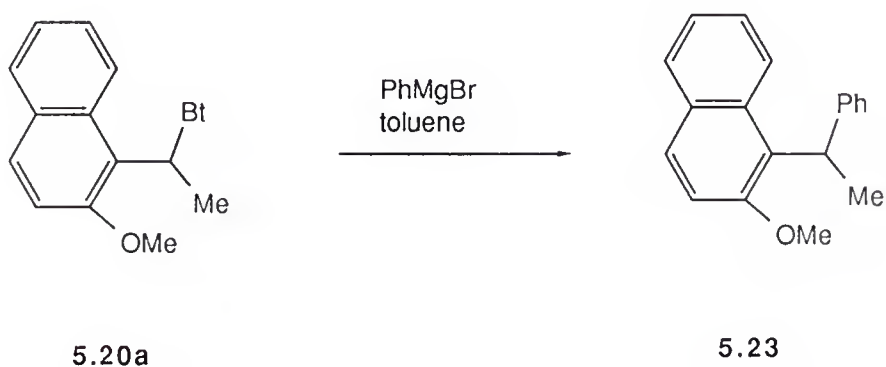
No reaction of 5.7c occurred with phenylmagnesium bromide in refluxing THF. However, under conditions of refluxing toluene [90JCS(P1)1717, 89JOC6022], 5.7c reacted with phenyl- and benzyl-magnesium bromides to give the desired products 5.22a and 5.22b in yields of 56% and 13%, respectively (Scheme 5.7).



Scheme 5.7

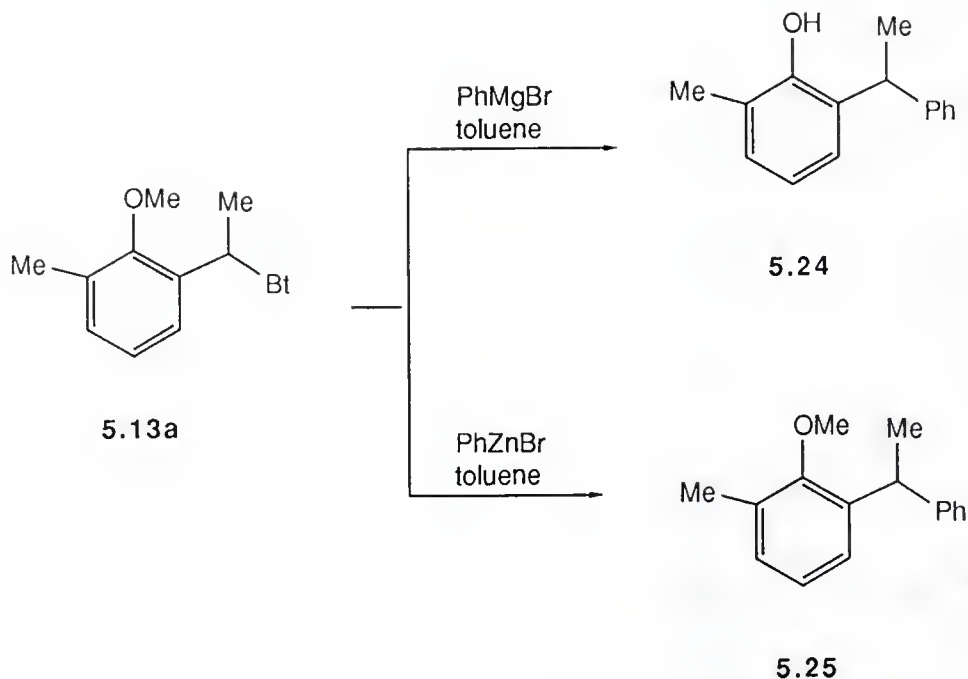
The naphthyl derivative 5.7f did not react with phenylmagnesium bromide in THF at room temperature, or under reflux, or in toluene under reflux for 2 days. However, the introduction of a substituent at the

methylene carbon enhanced the reactivity. Thus compound 5.20a and phenylmagnesium bromide in refluxing toluene gave the desired product 5.23 in a yield of 69% (Scheme 5.8).



Scheme 5.8

Similarly, while compound 5.12 was unaffected by Grignard reagents, its methyl derivative 5.13a reacted quite readily. With phenylmagnesium bromide, product 5.24 was obtained in which benzotriazole has been displaced and the methoxy group simultaneously demethylated. The use of the milder reagent phenylzinc bromide avoided the demethylation and gave compound 5.25 in a yield of 75% (Scheme 5.9).



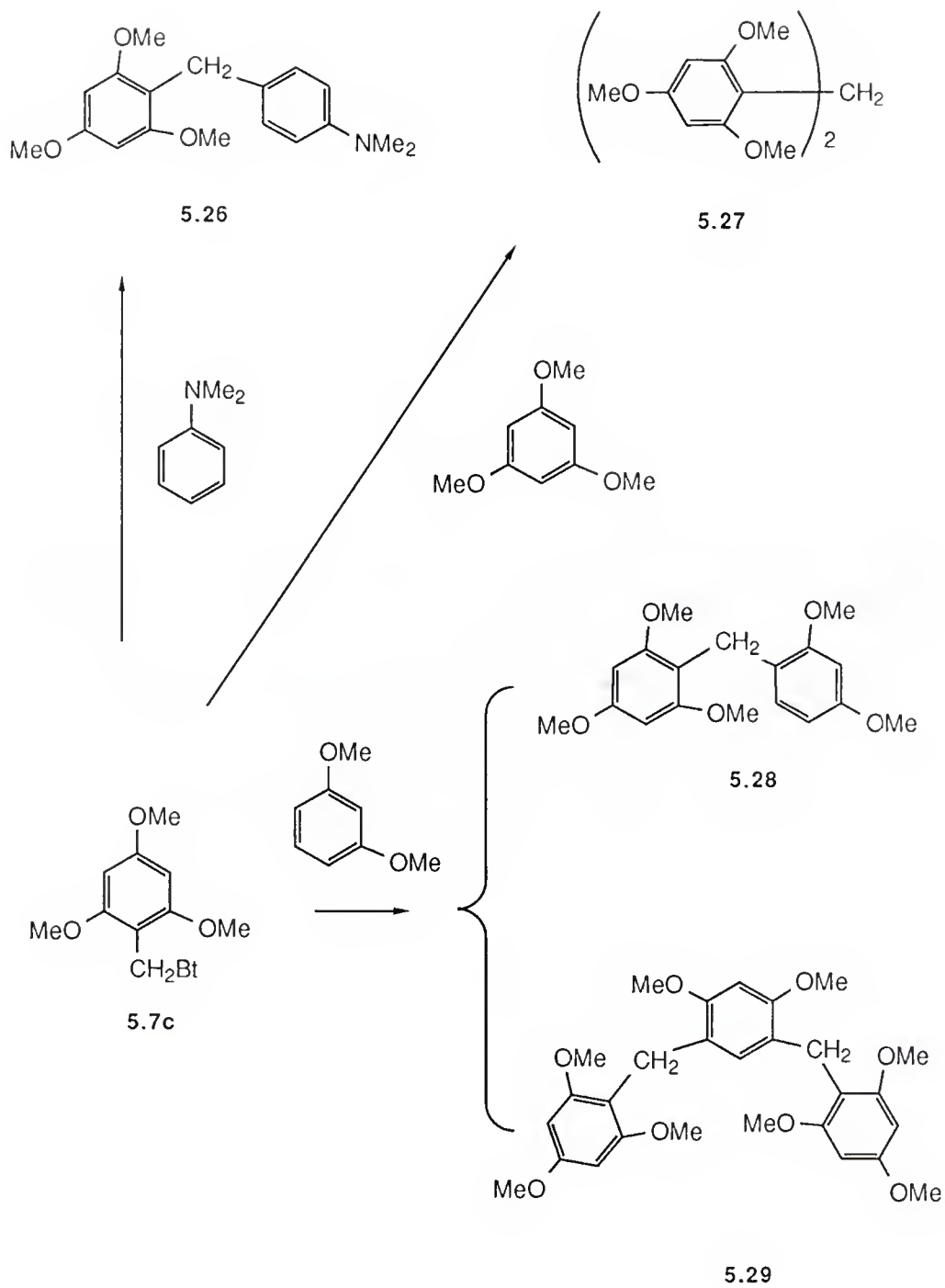
Scheme 5.9

5.2.3.2 By Electron-rich Aromatic and Heteroaromatic Compounds

For 4-(benzotriazol-1-ylmethyl)-N,N-dialkylanilines, we have demonstrated (see Chapters II-III) that the benzotriazole group can be displaced by electron-rich aromatic nucleophiles including anilines, 1,3-dimethoxybenzene, 1,3,5-trimethoxybenzene, pyrroles, and indoles. These same nucleophiles similarly displace the benzotri-

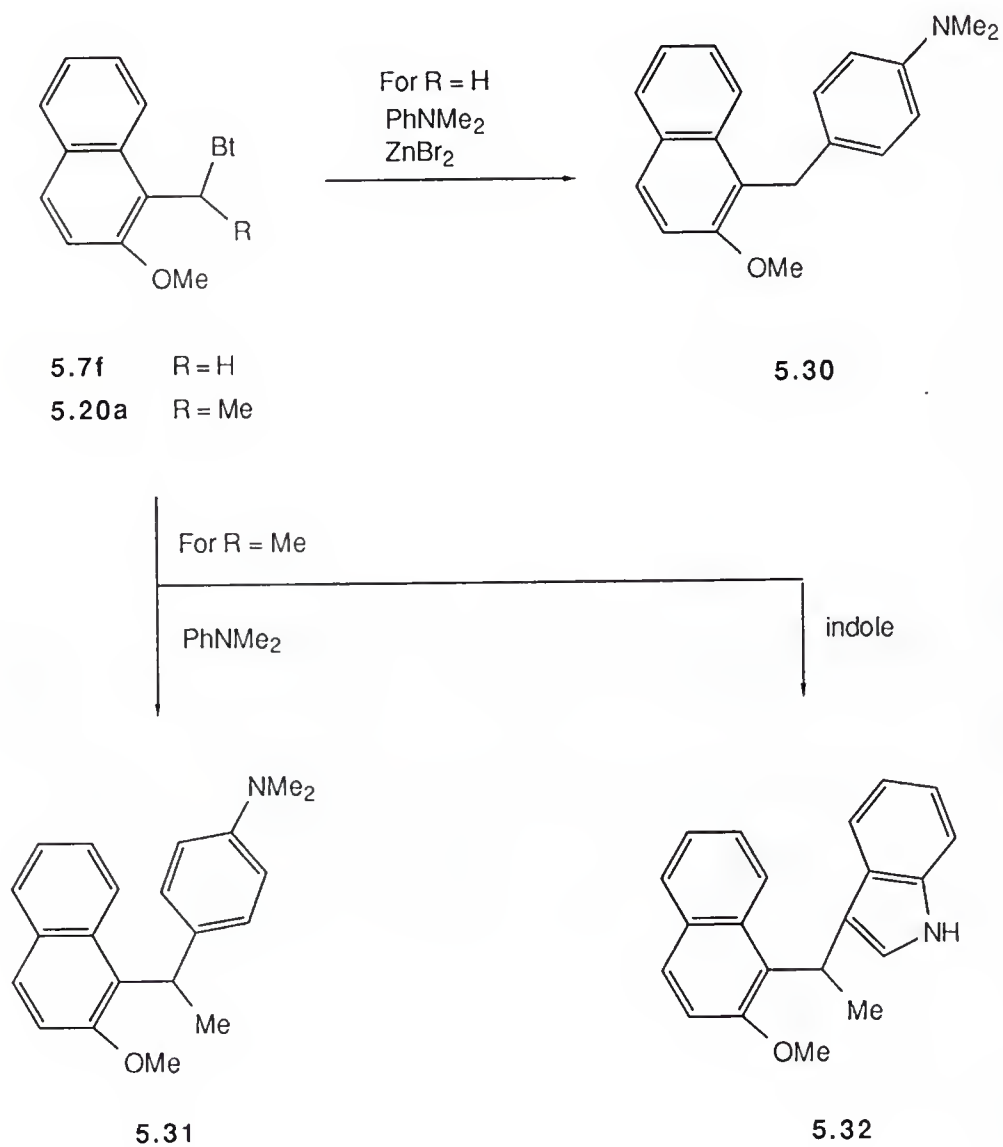
azolyl moiety in the present compounds. Thus, 5.7c was found to give products 5.26 and 5.27 when reacted with *N,N*-dimethylaniline and 1,3,5-trimethoxybenzene, respectively. With 1,3-dimethoxybenzene, in addition to the monosubstituted product 5.28 (38%), the disubstituted analogue 5.29 (48%) was also obtained (Scheme 5.10).

The reaction between 5.7f and *N,N*-dimethylaniline required vigorous conditions such as anhydrous zinc bromide in refluxing toluene to give 5.30. However, similar to the displacement by Grignard reagents, the presence of a substituent at the methylene carbon enhanced the reactivity in this displacement also. As a result, the reactions of 5.20a with *N,N*-dimethylaniline and indole occurred under much milder conditions (reflux in 50% aqueous methanol solution) to give the desired products 5.31 and 5.32, respectively (Scheme 5.11). With indole, 2-methoxynaphthalene was also isolated. This was the major product in the reaction of 5.20a with 1,3-dimethoxybenzene, and the only product with 1,3,5-trimethoxybenzene. Heating 5.20a alone under the same reaction conditions also gave 2-methoxynaphthalene. In another experiment, when a mixture of 5.20a, indole, and zinc bromide was heated to 140 °C for 5 h, 2-methoxynaphthalene was again obtained. It may thus be concluded that due to steric crowding, compound 5.20a is not stable under vigorous reaction conditions, and dissociates to



Scheme 5.10

2-methoxynaphthalene. It is reported [55JA5756] that 1,1'-benzal-bis(2-methoxynaphthalene) is readily hydrolyzed under acidic conditions with the cleavage of the C-C bond to yield benzaldehyde and 2-methoxynaphthalene.



Scheme 5.11

Table 5.3 Displacement of Benzotriazole from the (Benzotriazolylalkyl)phenyl Methyl Ethers By Grignard Reagents and Aromatic Nucleophiles

Substrate	Reagent ^a	Product	React. time (h)	Yield ^b (%)	M.p. (°C)	Purification ^c
5.5e	5.6	5.8	1	46	151-153 ^d	10:1
5.7f	2-MN	5.9	5	73	145-147 ^e	10:1
5.7c	PhMgBr	5.22a	8	56	93-95 ^f	20:1
5.7c	PhCH ₂ MgBr	5.22b	8	13	oil	1:2 ^g
5.20a	PhMgBr	5.23	24	69	70-72	hexane
5.13a	PhMgBr	5.24	48	38	oil ^h	12:1
5.13a	PhZnBr	5.25	72	75	oil	40:1
5.7c	DMA	5.26	23	70	89-90 ⁱ	hexane ^j
5.7c	TMB	5.27	30	40	116-117 ^k	9:1
5.7c	DMB	5.28	24	38	146-148	9:1
5.7c	DMB	5.29	24	48	157-159	9:1
5.7f	DMA	5.30	12	83	107-109	8:1
5.20a	DMA	5.31	72	52	oil	10:1
5.20a	Indole	5.32	24	43	45-47	10:1

^a MN = methoxynaphthalene; DMA = N,N-dimethylaniline; TMB = 1,3,5-trimethoxybenzene; DMB = 1,3-dimethoxybenzene.

^b Isolated yields.

^c Purified by column chromatography. The ratio indicates that of eluent, petroleum ether (38-56 °C)/EtOAc, v/v.

^d Lit. [56JOC1310] m.p. 150.5-152 °C.

^e Lit. [36JOC265] m.p. 146-147 °C.

^f Lit. [76CCC1777] m.p. 92-94 °C.

^g hexane/CH₂Cl₂.

^h Lit. [57AG699] b.p. 166 °C/10 torr.

ⁱ Lit. [Chapter III] m.p. 89-90 °C.

^j Purified by recrystallization.

^k Lit. [39JCS89] m.p. 116-117 °C.

5.3 Conclusions

Methoxy-benzenes and -naphthalenes are benzotriazolylmethylated in the para-position or if this is blocked in the ortho-position. The methylene groups in the products are readily substituted by electrophiles via the lithiated derivatives. Displacement of the benzotriazolyl moiety by organometallic reagents, or by electron-rich benzenoid compounds provides a versatile method for the synthesis of substituted aryl ethers.

5.4 Experimental

The apparatus and general procedures applied in this Chapter are identical to those described in Chapters II and III with the following additions.

NMR spectra were recorded on a VXR 300 spectrometer [^1H -NMR (300 MHz); ^{13}C -NMR (75 MHz)] or as specified individually on a XL 200 spectrometer [^1H -NMR (200 MHz); ^{13}C -NMR (50 MHz)].

Column chromatography was carried out on MBS silica gel (230-400 mesh).

5.4.1 General Procedure for the Alkylation of Phenol Ethers

A mixture of 1-hydroxymethylbenzotriazole (1.49 g, 10 mmol), the appropriate phenol ether (10 mmol), and

p-toluenesulfonic acid (1.90 g, 10 mmol) in toluene (60 ml) [acetic acid (30 ml) was used both as the solvent and the acid catalyst for 5.5c] was heated under reflux for the appropriate time. The solvent was then removed under reduced pressure and to the residue was added sodium hydrogen carbonate solution (10%; 30 ml). The product was extracted with diethyl ether (3 × 30 ml), the organic extract washed with water (30 ml), and dried (MgSO₄). The solvent was removed in vacuo, and the residue purified.

Physical data of the products, reaction time, yields, and methods of purification are given in Table 5.1. Further purification for the analytically pure sample is described for the particular compound.

4-(Benzotriazol-1-ylmethyl)anisole (5.7a). Obtained as microcrystals (recrystallized from hexane/benzene). ¹H NMR δ 3.74 (s, 3 H), 5.75 (s, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 7.22 (d, J = 8.6 Hz, 2 H), 7.3–7.4 (m, 3 H), 8.03 (d, J = 8.1 Hz, 1 H); ¹³C NMR δ 51.7, 55.1, 109.7, 114.2, 119.8, 123.7, 126.7, 127.2, 129.0, 132.6, 146.2, 159.5.

Anal. Calcd for C₁₄H₁₃N₃O: C, 70.28; H, 5.48; N, 17.56. Found: C, 70.02; H, 5.47; N, 17.81.

4-(Benzotriazol-1-ylmethyl)-1,3-dimethoxybenzene (5.7b). Obtained as prisms (recrystallized from

hexane/benzene). ^1H NMR δ 3.69 (s, 3 H), 3.75 (s, 3 H), 5.72 (s, 2 H), 6.3–6.4 (m, 2 H), 7.06 (d, J = 8.3 Hz, 1 H), 7.25–7.40 (m, 2 H), 7.46 (d, J = 8.3 Hz, 1 H), 7.98 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ 46.1, 54.9, 55.0, 98.1, 104.2, 109.9, 115.2, 119.2, 123.3, 126.6, 130.2, 132.6, 145.6, 157.7, 160.9.

Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.67; H, 5.59; N, 15.65.

2-(Benzotriazol-1-ylmethyl)-1,3,5-trimethoxybenzene (5.7c). Obtained as microcrystals (recrystallized from aqueous ethanol). ^1H NMR δ 3.77 (s, 3 H), 3.79 (s, 6 H), 5.81 (s, 2 H), 6.11 (s, 2 H), 7.25 (t, J = 8.0 Hz, 1 H), 7.34 (t, J = 8.0 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.97 (d, J = 8.0 Hz, 1 H); ^{13}C NMR δ 41.0, 55.2, 55.6, 90.3, 103.4, 110.4, 119.2, 123.1, 126.3, 132.8, 145.6, 159.6, 161.8.

Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.01; H, 5.84; N, 13.78.

2-(Benzotriazol-1-ylmethyl)-4-methylanisole (5.7d). Obtained as plates (recrystallized from hexane/benzene). ^1H NMR (200 MHz) δ 2.16 (s, 3 H), 3.81 (s, 3 H), 5.79 (s, 2 H), 6.76 (d, J = 8.2 Hz, 1 H), 6.92 (s, 1 H), 7.04 (d, J = 8.2 Hz, 1 H), 7.26–7.52 (m, 3 H), 8.02 (dd, J = 9.0, 1.0 Hz, 1 H); ^{13}C NMR (50 MHz) δ 20.2, 46.4, 55.3, 110.0,

110.4, 119.6, 122.7, 123.5, 126.9, 129.2, 130.0, 132.9, 145.9, 154.6.

Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.48; H, 6.04; N, 16.70.

Reaction of 1-methoxynaphthalene (5.5e) with 5.6. A mixture of 5.7e (30%) and bis(4-methoxynaphthalen-1-yl)methane (5.8) (46%) was obtained.

4-(Benzotriazol-1-ylmethyl)-1-methoxynaphthalene (5.7e). Obtained as microcrystals (recrystallized from chloroform). ^1H NMR (200 MHz) δ 3.96 (s, 3 H), 6.18 (s, 2 H), 6.73 (d, J = 7.9 Hz, 1 H), 7.2–7.35 (m, 4 H), 7.42–7.55 (m, 2 H), 7.95–8.15 (m, 2 H), 8.25–8.32 (m, 1 H); ^{13}C NMR (50 MHz) δ 51.0, 55.5, 102.7, 110.1, 119.9, 121.7, 122.7, 122.8, 123.7, 125.5, 125.9, 127.1, 127.4, 127.6, 132.1, 133.0, 146.3, 156.3.

Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.60; H, 5.23; N, 14.67.

Bis(4-methoxynaphthalen-1-yl)methane (5.8). Obtained as plates (recrystallized from hexane/benzene). ^1H NMR (200 MHz) δ 3.86 (s, 6 H), 4.63 (s, 2 H), 6.56 (d, J = 7.9 Hz, 2 H), 6.89 (d, J = 7.9 Hz, 2 H), 7.4–7.5 (m, 4 H), 7.9–8.0 (m, 2 H), 8.3–8.4 (m, 2 H); ^{13}C NMR (50 MHz) δ 34.7, 55.3, 103.4, 122.5, 123.8, 124.9, 125.8, 126.4, 126.8, 128.2, 133.0, 154.3.

Reaction of 2-methoxynaphthalene (5.5f) with 5.6. A mixture of 1-(benzotriazol-1-ylmethyl)-2-methoxynaphthalene (5.7f) (50%) and bis(2-methoxynaphthalen-1-yl)methane (5.9) (18%) was obtained.

1-(Benzotriazol-1-ylmethyl)-2-methoxynaphthalene (5.7f). Obtained as microcrystals (recrystallized from hexane/benzene). ^1H NMR δ 4.08 (s, 3 H), 6.33 (s, 2 H), 7.2–7.3 (m, 4 H), 7.46–7.54 (m, 2 H), 7.72–7.76 (m, 1 H), 7.86 (d, $J = 9.2$ Hz, 1 H), 7.95 (dt, $J = 8.0, 1.3$ Hz, 1 H), 8.37 (dd, $J = 8.6, 0.8$ Hz, 1 H); ^{13}C NMR δ 43.0, 56.5, 110.4, 112.5, 114.4, 119.6, 123.1, 123.5, 123.9, 126.8, 127.6, 128.4, 129.1, 131.4, 132.8, 133.2, 146.0, 155.2.

Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.85; H, 5.26; N, 14.78.

Bis(2-methoxynaphthalen-1-yl)methane (5.9). Obtained as microcrystals (recrystallized from hexane/benzene). ^1H NMR (200 MHz) δ 3.79 (s, 6 H), 4.89 (s, 2 H), 7.1–7.3 (m, 6 H), 7.6–7.7 (m, 4 H), 8.17 (d, $J = 8.4$ Hz, 2 H); ^{13}C NMR (50 MHz) δ 21.6, 56.6, 113.8, 123.0, 123.7, 124.4, 125.7, 127.9, 128.2, 129.4, 133.7, 154.5.

5.4.2 General Procedure for the Conversion of the Phenol Derivatives 5.11 and 5.19 to the Corresponding Methyl Ethers 5.12 and 5.7f

To a solution of the appropriate phenol derivative (10 mmol) in dimethyl sulfoxide (20 ml) was added sodium

hydride (60% in mineral oil; 0.48 g, 12 mmol). The solution was stirred at room temperature for 30 min and methyl iodide (1.25 ml, 20 mmol) was added. The solution was stirred for an additional 10 min, poured into ice-water (40 ml) and extracted with diethyl ether (3 × 50 ml). The combined extract was washed with water (4 × 50 ml), dried (MgSO₄), and the solvent evaporated to give the essentially pure product.

1-(Benzotriazol-1-ylmethyl)-2-methoxynaphthalene (5.7f). It was obtained from 5.19 in 90% yield. It is identical in all aspects with the sample prepared earlier.

2-(Benzotriazol-1-ylmethyl)-6-methylanisole (5.12). Obtained as plates (recrystallized from hexane/benzene). ¹H NMR δ 2.30 (s, 3 H), 3.72 (s, 3 H), 5.86 (s, 2 H), 6.90 (d, J = 5.2 Hz, 2 H), 7.05–7.15 (m, 1 H), 7.25–7.50 (m, 3 H), 8.02 (dt, J = 8.3, 1.1 Hz, 1 H); ¹³C NMR δ 15.9, 47.0, 60.6, 109.8, 119.6, 123.6, 124.2, 126.9, 127.1, 127.6, 131.2, 131.7, 132.7, 145.9, 156.2.

Anal. Calcd for C₁₅H₁₅N₃O: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.38; H, 6.00; N, 16.38.

5.4.3 General Procedure for the Lithiation of 5.7 and 5.12

To a solution of the appropriate substrate (1 mmol) in THF (20 ml) at -78 °C was added n-BuLi (2.5 M in

hexane; 0.4 ml, 1 mmol). The resulting solution was stirred at -78°C for 2 h, then the electrophile (1 mmol) in THF (3 ml) was added. After allowing to reach room temperature, stirring was continued overnight and the solution was diluted with water and extracted with diethyl ether (3×30 ml). The combined extract was washed with water (30 ml) and dried (MgSO_4). The solvent was removed in vacuo and the residue purified.

Physical data of the products, substrates, electrophiles, yields, and methods of purification are given in Table 5.2. Further purification for the analytically pure sample is described for the particular compound.

4-[1-(Benzotriazol-1-yl)ethyl]anisole (5.10a).

Obtained as microcrystals (recrystallized from hexane/benzene). ^1H NMR δ 2.11 (d, $J = 7.1$ Hz, 3 H), 3.73 (s, 3 H), 6.00 (q, $J = 7.1$ Hz, 1 H), 6.82 (d, $J = 8.8$ Hz, 2 H), 7.2–7.3 (m, 5 H), 8.0–8.1 (m, 1 H); ^{13}C NMR δ 20.9, 55.0, 58.4, 110.1, 114.0, 119.7, 123.6, 126.8, 127.4, 131.9, 132.2, 146.2, 159.2.

Anal. Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}$: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.96; H, 5.98; N, 16.49.

1-(Benzotriazol-1-yl)-1-(4-methoxyphenyl)-2-phenylethane (5.10b). Obtained as prisms (recrystallized

from hexane/benzene). ^1H NMR (200 MHz) δ 3.71 (dd, J = 13.8, 6.8 Hz, 1 H), 3.73 (s, 3 H), 4.08 (dd, J = 13.8, 8.7 Hz, 1 H), 5.91 (dd, J = 8.7, 6.8 Hz, 1 H), 6.75–6.85 (m, 2 H), 7.0–7.4 (m, 10 H), 7.95–8.05 (m, 1 H); ^{13}C NMR (50 MHz) δ 41.4, 55.1, 64.7, 109.6, 114.1, 119.8, 123.7, 126.7, 126.9, 128.2, 128.3, 129.0, 130.8, 132.8, 137.2, 146.0, 159.4.

Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.42; H, 5.82; N, 12.63.

2-(Benzotriazol-1-yl)-2-(4-methoxyphenyl)-1,1-diphenylethanol (5.10c). Obtained as microcrystals (recrystallized from hexane/benzene). ^1H NMR (200 MHz) δ 3.66 (s, 3 H), 5.83 (s, 1 H), 6.59 (d, J = 8.3 Hz, 3 H), 6.9–7.5 (m, 14 H), 7.98 (d, J = 8.2 Hz, 1 H); ^{13}C NMR (50 MHz) δ 55.0, 68.0, 81.2, 109.3, 113.0, 120.2, 124.4, 125.4, 126.4, 126.8, 126.9, 127.1, 127.7, 128.0, 128.2, 130.1, 133.2, 143.1, 144.8, 145.4, 159.2.

Anal. Calcd for $\text{C}_{27}\text{H}_{23}\text{N}_3\text{O}_2$: C, 76.94; H, 5.50; N, 9.97. Found: C, 76.86; H, 5.53; N, 9.94.

2-(Benzotriazol-1-yl)-2-(4-methoxyphenyl)acetic acid (5.10d). Obtained as microcrystals (recrystallized from methanol/EtOAc). ^1H NMR (200 MHz) δ 3.76 (s, 3 H), 7.00 (d, J = 8.1 Hz, 2 H), 7.15 (s, 1 H), 7.35–7.74 (m, 5 H), 8.07 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (50 MHz) δ 55.2, 63.7,

111.0, 114.1, 119.2, 124.0, 125.9, 127.5, 130.6, 132.8, 145.2, 159.5, 169.5.

Anal. Calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 63.33; H, 4.63; N, 14.77.

2-[1-(Benzotriazol-1-yl)ethyl]-6-methylanisole

(5.13a). Evaporation of solvent gave the essentially pure product as microcrystals. ^1H NMR δ 2.16 (d, $J = 7.0$ Hz, 3 H), 2.32 (s, 3 H), 3.73 (s, 3 H), 6.40 (q, $J = 7.0$ Hz, 1 H), 6.97 (t, $J = 7.6$ Hz, 1 H), 7.13 (t, $J = 7.6$ Hz, 2 H), 7.24-7.44 (m, 3 H), 8.02 (d, $J = 8.3$ Hz, 1 H); ^{13}C NMR δ 16.3, 21.2, 52.5, 60.9, 110.1, 119.8, 123.7, 124.5, 125.0, 126.9, 131.1, 131.5, 132.6, 133.1, 146.1, 155.6.

Anal. Calcd for $C_{16}H_{17}N_3O$: C, 71.89; H, 6.41; N, 15.71. Found: C, 72.03; H, 6.46; N, 15.70.

1-(Benzotriazol-1-yl)-1-(2-methoxy-3-methylphenyl)-1-phenylethane (5.13b). Obtained as plates (recrystallized from hexane/benzene). ^1H NMR δ 2.25 (s, 3 H), 3.46 (s, 3 H), 3.72 (dd, $J = 14.0, 6.4$ Hz, 1 H), 4.09 (dd, $J = 14.0, 8.9$ Hz, 1 H), 6.40 (dd, $J = 8.9, 6.4$ Hz, 1 H), 6.9-7.3 (m, 9 H), 7.40 (dd, $J = 8.0, 0.8$ Hz, 1 H), 7.48 (d, $J = 7.8$ Hz, 1 H), 7.94 (dd, $J = 8.0, 1.0$ Hz, 1 H); ^{13}C NMR δ 16.3, 41.2, 58.1, 60.6, 109.6, 119.4, 123.6, 124.4, 125.6, 126.6, 126.8, 128.3, 129.1, 130.8, 131.6, 133.1, 137.5, 145.6, 155.7.

Anal. Calcd for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.16; N, 12.24. Found: C, 77.03; H, 6.26; N, 12.33.

2-(Benzotriazol-1-yl)-2-(2-methoxy-3-methylphenyl)-1-(4-methylphenyl)ethanol (5.13c). Purification of the crude product by column chromatography (see Table 5.2) gave isomer I (25%) as microcrystals, isomer II (36%) as microcrystals, and a mixture of both isomers (26%). The total yield was 87%.

Isomer I. ^1H NMR δ 2.19 (s, 3 H), 2.28 (s, 3 H), 3.36 (d, $J = 2.7$ Hz, 1 H), 3.53 (s, 3 H), 5.98 (dd, $J = 7.4$, 2.7 Hz, 1 H), 6.34 (d, $J = 7.4$ Hz, 1 H), 6.95 (d, $J = 8.0$ Hz, 2 H), 7.06 (t, $J = 7.6$ Hz, 1 H), 7.1-7.4 (m, 6 H), 7.80 (dd, $J = 7.6$, 1.6, Hz, 1 H), 7.90 (d, $J = 8.2$ Hz, 1 H); ^{13}C NMR δ 16.5, 21.0, 60.7, 60.8, 75.2, 109.7, 119.5, 123.8, 124.4, 126.7, 127.0, 127.2, 128.6, 128.9, 130.8, 132.0, 133.1, 137.1, 137.9, 145.0, 156.9.

Anal. Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 74.10; H, 6.32; N, 11.29.

Isomer II. ^1H NMR δ 2.16 (s, 3 H), 2.23 (s, 3 H), 3.20 (s, 3 H), 4.22 (d, $J = 4.9$ Hz, 1 H), 6.05 (dd, $J = 8.8$, 4.9 Hz, 1 H), 6.32 (d, $J = 8.8$ Hz, 1 H), 6.92 (t, $J = 7.7$ Hz, 1 H), 7.00 (d, $J = 8.3$ Hz, 3 H), 7.19 (d, $J = 8.3$ Hz, 2 H), 7.25 (td, $J = 8.1$, 1.3 Hz, 1 H), 7.34 (dt, $J =$

8.3, 1.0 Hz, 1 H), 7.46 (dd, $J = 7.6, 1.1$ Hz, 1 H), 7.55 (d, $J = 8.4$ Hz, 1 H), 7.90 (d, $J = 8.3$ Hz, 1 H); ^{13}C NMR δ 16.5, 21.0, 60.3, 62.8, 75.1, 110.1, 119.4, 124.0, 124.1, 126.6, 126.9, 127.3, 128.7, 129.0, 130.7, 131.8, 133.6, 136.9, 137.4, 145.2, 156.0.

Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 74.10; H, 6.32; N, 11.29.

1-[(Benzotriazol-1-yl)-(2-methoxy-3-methylphenyl)]-methyl-1-cyclohexanol (5.13d). Obtained as plates (recrystallized from methanol). ^1H NMR δ 1.1-1.7 (m, 10 H), 2.33 (s, 3 H), 3.75 (d, $J = 1.5$ Hz, 1 H), 3.90 (s, 3 H), 6.25 (s, 1 H), 7.00 (t, $J = 7.6$ Hz, 1 H), 7.10 (dd, $J = 7.5, 1.0$ Hz, 1 H), 7.35 (dt, $J = 8.2, 0.9$ Hz, 1 H), 7.48 (dt, $J = 6.9, 0.9$ Hz, 1 H), 7.69 (d, $J = 8.4$ Hz, 1 H), 7.92 (dd, $J = 7.8, 1.4$ Hz, 1 H), 8.05 (td, $J = 8.4, 0.9$ Hz, 1 H); ^{13}C NMR δ 16.9, 21.2, 21.5, 34.6, 36.3, 61.1, 62.7, 74.6, 109.8, 120.0, 124.0, 124.1, 127.6, 128.0, 128.7, 130.0, 131.7, 134.0, 144.9, 156.5.

Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_2$: C, 71.77; H, 7.17; N, 11.96. Found: C, 71.90; H, 7.33; N, 12.06.

2-(Benzotriazol-1-yl)-2-(2-methoxy-3-methylphenyl)-1,1-diphenylethanol (5.13e). Obtained as plates (recrystallized from methanol). ^1H NMR δ 2.15 (s, 3 H), 3.07 (s, 3 H), 5.93 (s, 1 H), 6.9-7.5 (m, 15 H), 7.67 (td,

$J = 8.4, 1.1 \text{ Hz}, 1 \text{ H}$), 7.90 (td, $J = 8.4, 0.9 \text{ Hz}, 1 \text{ H}$), 7.95 (dd, $J = 7.8, 1.5 \text{ Hz}, 1 \text{ H}$); ^{13}C NMR δ 17.1, 59.9, 60.3, 81.7, 109.8, 119.9, 123.6, 124.2, 125.8, 127.1, 127.2, 127.5, 127.6, 127.8, 128.1, 128.5, 128.8, 129.6, 132.0, 133.3, 143.0, 144.5, 145.2, 156.3.

Anal. Calcd for $\text{C}_{28}\text{H}_{25}\text{N}_3\text{O}_2$: C, 77.22; H, 5.79; N, 9.65. Found: C, 77.51; H, 5.85; N, 9.71.

2-(Benzotriazol-1-yl)-2-(2-methoxy-3-methylphenyl)-acetophenone (5.13f). Obtained as microcrystals. ^1H NMR δ 2.30 (s, 3 H), 3.43 (s, 3 H), 6.99 (t, $J = 7.7 \text{ Hz}, 1 \text{ H}$), 7.20 (t, $J = 8.0 \text{ Hz}, 2 \text{ H}$), 7.25–7.52 (m, 6 H), 7.95–8.05 (m, 3 H), 8.16 (s, 1 H); ^{13}C NMR δ 16.3, 60.5, 62.8, 110.8, 119.9, 123.7, 124.1, 126.0, 127.4, 127.7, 128.6, 128.7, 131.9, 133.2, 133.8, 134.1, 146.2, 156.6, 192.4.

Anal. Calcd for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.71; H, 5.31; N, 11.70.

(Benzotriazol-1-yl)-(2,4,6-trimethoxyphenyl)mono-deuteriomethane (5.15a). Evaporation of solvent gave the essentially pure product as needles. ^1H NMR δ 3.76 (s, 3 H), 3.78 (s, 6 H), 5.79 (s, 1 H), 6.11 (s, 2 H), 7.25 (t, $J = 8.0 \text{ Hz}, 1 \text{ H}$), 7.34 (t, $J = 8.0 \text{ Hz}, 1 \text{ H}$), 7.51 (d, $J = 8.0 \text{ Hz}, 1 \text{ H}$), 7.97 (d, $J = 8.0 \text{ Hz}, 1 \text{ H}$); ^{13}C NMR δ 40.8, 55.1, 55.5, 90.3, 103.3, 110.4, 119.2, 123.0, 126.3, 132.8, 145.6, 159.5, 161.7. MS (HR) for $\text{C}_{16}\text{H}_{16}\text{DN}_3\text{O}_3$ Calcd: 300.1333. Found: 300.1336.

2-[1-(Benzotriazol-1-yl)ethyl]-1,3,5-trimethoxy-
benzene (5.15b). Obtained as plates (recrystallized from
 hexane/benzene). ^1H NMR (200 MHz) δ 2.24 (d, $J = 7.1$ Hz, 3
 H), 3.67 (s, 6 H), 3.77 (s, 3 H), 6.09 (s, 2 H), 6.42 (q,
 $J = 7.1$ Hz, 1 H), 7.2–7.3 (m, 3 H), 7.95–8.05 (m, 1 H);
 ^{13}C NMR (50 MHz) δ 17.9, 50.5, 55.2, 55.6, 90.8, 108.7,
 110.5, 119.3, 123.0, 126.0, 132.9, 145.9, 159.0, 161.1.

Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_3$: C, 65.16; H, 6.11; N,
 13.41. Found: C, 65.09; H, 6.15; N, 13.42.

1-[1-(Benzotriazol-1-yl)-1-(2,4,6-trimethoxy-
phenyl)]methyl-1-cyclohexanol (5.15c). Obtained as
 microcrystals (recrystallized from EtOH/EtOAc). ^1H NMR
 (200 MHz) δ 1.2–2.1 (m, 10 H), 3.75 (s, 6 H), 3.81 (s, 3
 H), 4.85 (s, 1 H), 6.1–6.2 (broad, 2 H), 6.33 (s, 1 H),
 7.25–7.40 (m, 3 H), 7.95–8.05 (m, 1 H); ^{13}C NMR (50 MHz) δ
 21.5, 21.8, 25.9, 34.8, 36.4, 55.2, 55.8, 62.2, 74.5,
 90.5, 105.5, 119.4, 123.4, 126.7, 133.9, 144.5, 159.0,
 161.1.

Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_4$: C, 66.48; H, 6.85; N,
 10.57. Found: C, 66.23; H, 6.84; N, 10.91.

Reaction of 5.7c with benzyl bromide. Purification of
 the crude product gave a mixture of 5.15d, 5.17, and 5.18
 in yields of 64%, 10%, and 12%, respectively (see Table
 5.2).

1-(Benzotriazol-1-yl)-1-(2,4,6-trimethoxyphenyl)-2-phenylethane (5.15d). Obtained as plates (recrystallized from hexane/benzene). ^1H NMR δ 3.58 (s, 6 H), 3.73 (s, 3 H), 3.98 (dd, $J = 13.5, 8.8$ Hz, 1 H), 4.31 (dd, $J = 13.5, 6.6$ Hz, 1 H), 6.00 (s, 2 H), 6.50 (dd, $J = 8.8, 6.6$ Hz, 1 H), 7.1–7.3 (m, 8 H), 7.95–8.05 (m, 1 H); ^{13}C NMR δ 37.6, 55.1, 55.7, 56.1, 90.9, 107.2, 110.4, 119.3, 123.1, 126.1, 127.9, 129.4, 133.1, 138.6, 145.8, 159.4, 161.2.

Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_3$: C, 70.93; H, 5.95; N, 10.79. Found: C, 70.64; H, 5.96; N, 10.68.

Trans-1-Phenyl-2-(2,4,6-trimethoxyphenyl)ethene (5.17). Obtained as plates (recrystallized from hexane/benzene), m.p. 58–59 °C (Lit. [74JCS(P1)2447] m.p. 58–59 °C). ^1H NMR δ 3.78 (s, 3 H), 3.83 (s, 6 H), 6.13 (s, 2 H), 7.12–7.22 (m, 1 H), 7.30 (t, $J = 7.9$ Hz, 2 H), 7.43 (d, $J = 7.3$ Hz, 2 H), 7.50 (d, $J = 7.3$ Hz, 2 H); ^{13}C NMR δ 55.1, 55.6, 90.7, 108.0, 119.8, 126.0, 126.4, 128.3, 129.7, 139.6, 159.4, 160.1.

1-Benzylbenzotriazole (5.18). Obtained as plates (recrystallized from hexane/benzene), m.p. 115–117 °C (Lit. [79HCA2129] m.p. 115–116 °C). ^1H NMR δ 5.83 (s, 2 H), 7.2–7.4 (m, 8 H), 8.05 (dt, $J = 8.0, 1.0$ Hz, 1 H); ^{13}C NMR δ 52.1, 109.6, 119.9, 123.8, 127.3, 127.5, 128.5, 128.9, 132.7, 134.7, 146.2.

1-[1-(Benzotriazol-1-yl)ethyl]-2-methoxynaphthalene (5.20a). Evaporation of solvent gave the essentially pure product as microcrystals. ^1H NMR δ 2.45 (d, J = 7.2 Hz, 3 H), 3.94 (s, 3 H), 6.92 (q, J = 7.2 Hz, 1 H), 7.0–7.3 (m, 6 H), 7.71 (dd, J = 8.0, 1.4 Hz, 1 H), 7.81 (d, J = 9.0 Hz, 1 H), 7.97 (dt, J = 7.8, 1.4 Hz, 1 H), 8.02 (d, J = 9.0 Hz, 1 H); ^{13}C NMR δ 18.7, 52.0, 56.5, 110.3, 112.9, 119.5, 119.7, 122.5, 123.5, 123.6, 126.5, 127.1, 128.9, 129.4, 130.8, 131.6, 133.2, 146.3, 154.3.

Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.10; H, 5.57; N, 14.01.

2-(Benzotriazol-1-yl)-2-(2-methoxynaphthalen-1-yl)-1-(4-methylphenyl)ethanol (5.20b). Obtained as microcrystals. ^1H NMR δ 2.17 (s, 3 H), 3.58 (s, 3 H), 4.57 (d, J = 2.5 Hz, 1 H), 6.6–6.7 (m, 1 H), 6.8–7.4 (m, 11 H), 7.67 (t, J = 9.0 Hz, 2 H), 8.00 (d, J = 8.0 Hz, 1 H), 8.04 (d, J = 9.0 Hz, 1 H); ^{13}C NMR δ 21.0, 56.5, 63.5, 73.4, 110.5, 112.9, 116.1, 119.6, 122.6, 123.5, 124.1, 126.7, 127.2, 127.3, 128.1, 128.8, 129.2, 131.2, 132.1, 133.6, 135.7, 137.3, 145.7, 155.2.

Anal. Calcd for $\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_2$: C, 76.26; H, 5.66; N, 10.26. Found: C, 75.96; H, 5.56; N, 10.20.

Reaction of 5.7f with benzyl bromide. Purification of the crude product gave 5.18, 5.20c, and 5.21 in yields of 14%, 16%, and 20%, respectively (see Table 5.2).

1-(Benzotriazol-1-yl)-1-(2-methoxynaphthalen-1-yl)-2-phenylethane (5.20c). Obtained as microcrystals. ^1H NMR δ 3.63 (s, 3 H), 4.16 (dd, $J = 13.6, 9.0$ Hz, 1 H), 4.60 (dd, $J = 13.6, 6.0$ Hz, 1 H), 7.0–7.4 (m, 12 H), 7.68 (d, $J = 8.0$ Hz, 1 H), 7.74 (d, $J = 9.0$ Hz, 1 H), 7.9–8.0 (m, 1 H), 8.23 (d, $J = 9.0$ Hz, 1 H); ^{13}C NMR δ 38.4, 56.7, 57.6, 110.3, 113.2, 118.2, 119.4, 122.9, 123.6, 126.4, 126.6, 127.1, 127.9, 128.8, 129.4, 129.5, 131.0, 131.9, 133.3, 137.9, 146.0, 155.0.

Anal. Calcd for $\text{C}_{25}\text{H}_{21}\text{N}_3\text{O}$: C, 79.13; H, 5.58; N, 11.07. Found: C, 78.80; H, 5.50; N, 11.11.

Trans-1-Phenyl-2-(2-methoxynaphthalen-1-yl)ethylene (5.21). Obtained as an oil. ^1H NMR δ 3.92 (s, 3 H), 7.1–7.5 (m, 8 H), 7.58 (d, $J = 6.8$ Hz, 2 H), 7.75 (t, $J = 6.8$ Hz, 2 H), 8.25 (d, $J = 6.8$ Hz, 1 H); ^{13}C NMR δ 56.3, 113.1, 120.5, 122.2, 123.5, 124.3, 126.4, 126.5, 127.4, 128.3, 128.6, 128.7, 129.3, 132.6, 134.8, 138.1, 154.7. MS (HR) for $\text{C}_{19}\text{H}_{16}\text{O}$ Calcd: 260.1201. Found: 260.1200.

5.4.4 General Procedure for the Displacement of Benzotriazole by Grignard Reagents

To a solution of the appropriate benzotriazole derivative (1 mmol) in toluene (20 ml) at room temperature was added the corresponding Grignard reagent (12 mmol) in diethyl ether. The solvent was distilled off until the

boiling point reached that of toluene and resulting solution was refluxed for the appropriate time until TLC indicated that the starting material had been consumed. The reaction mixture was poured into ice-water (20 ml), acidified with 2 N HCl, the mixture extracted with diethyl ether (3 x 30 ml) and the combined extract dried (MgSO₄). The solvent was removed in vacuo and the residue purified.

Physical data of the products, substrates, reagents, reaction time, yields, and methods of purification are given in Table 5.3.

2-Benzyl-1,3,5-trimethoxybenzene (5.22a). Obtained as microcrystals. ¹H NMR δ 3.69 (s, 6 H), 3.71 (s, 3 H), 3.93 (s, 2 H), 6.10 (s, 2 H), 7.0-7.2 (m, 5 H); ¹³C NMR δ 28.2, 55.1, 55.4, 90.4, 110.0, 125.1, 127.8, 128.3, 142.1, 158.7, 159.6.

2-Phenethyl-1,3,5-trimethoxybenzene (5.22b). Obtained as an oil. ¹H NMR δ 2.69-2.76 (m, 2 H), 2.84-2.90 (m, 2 H), 3.72 (s, 6 H), 3.77 (s, 3 H), 6.11 (s, 2 H), 7.0-7.3 (m, 5 H); ¹³C NMR δ 24.7, 35.7, 55.2, 55.5, 90.4, 110.9, 125.4, 127.9, 128.5, 143.1, 158.7, 159.2.

Anal. Calcd for C₁₇H₂₀O₃: C, 74.97; H, 7.40. Found: C, 75.01; H, 7.41.

1-(1-Phenylethyl)-2-methoxynaphthalene (5.23). Obtained as microcrystals. ¹H NMR δ 1.80 (d, J = 7.3 Hz, 3

H), 3.70 (s, 3 H), 5.26 (q, $J = 7.3$ Hz, 1 H), 7.1–7.3 (m, 8 H), 7.68–7.75 (m, 2 H), 7.84 (d, $J = 8.0$ Hz, 1 H); ^{13}C NMR δ 18.0, 34.4, 56.7, 114.6, 123.1, 124.4, 125.1, 125.8, 127.0, 127.9, 128.0, 128.4, 128.6, 129.9, 132.5, 146.0, 154.8.

Anal. Calcd for $\text{C}_{19}\text{H}_{18}\text{O}$: C, 86.99; H, 6.92. Found: C, 86.69; H, 7.01.

2-Methyl-6-(1-phenylethyl)phenol (5.24). Obtained as an oil. ^1H NMR δ 1.59 (d, $J = 7.2$ Hz, 3 H), 2.13 (s, 3 H), 4.30 (q, $J = 7.2$ Hz, 1 H), 4.59 (s, 1 H), 6.83 (t, $J = 7.6$ Hz, 1 H), 6.98 (dd, $J = 7.4, 0.8$ Hz, 1 H), 7.1–7.3 (m, 6 H); ^{13}C NMR δ 15.8, 21.2, 39.0, 120.3, 124.0, 125.5, 126.4, 127.4, 128.7, 128.9, 131.3, 145.3, 151.6.

2-Methyl-6-(1-phenylethyl)anisole (5.25). To phenylmagnesium bromide (1 mmol/ml in diethyl ether; 8 ml, 8 mmol) was added a solution of zinc bromide (3.6 g, 16 mmol) in THF (12 ml) to give a white precipitate. To the mixture was added 2-[1-(benzotriazol-1-yl)ethyl]-6-methylanisole (0.27 g, 1 mmol). Toluene (20 ml) was then added and the diethyl ether and THF were distilled off until the boiling point reached that of toluene. The resulting solution was then heated under reflux for 3 days (until TLC indicated that the starting material had been consumed), cooled, poured into ice-water (30 ml),

acidified with 2 N HCl and the mixture extracted with diethyl ether (3 × 30 ml). The combined extract was dried (MgSO₄), the solvent removed in vacuo, and the residue purified (see Table 5.3) to give 5.25 (0.17 g, 75%) as an oil. ¹H NMR δ 1.58 (d, J = 7.3 Hz, 3 H), 2.28 (s, 3 H), 3.57 (s, 3 H), 4.56 (q, J = 7.3 Hz, 1 H), 6.9–7.3 (m, 8 H); ¹³C NMR δ 16.3, 22.0, 37.6, 60.4, 123.9, 125.8, 125.9, 127.5, 128.2, 129.2, 130.9, 139.1, 146.7, 156.2. MS (HR) for C₁₆H₁₈O Calcd: 226.1357. Found: 226.1359.

5.4.5 General Procedure for the Displacement of Benzotriazole by Electron-rich Aromatic Compounds

To a solution of the substrate (1 mmol) in MeOH (20 ml) under reflux was added a solution of the appropriate aromatic nucleophile (1 mmol) and dilute hydrochloric acid (3%; 20 ml). The whole was then heated under reflux for the appropriate time followed by addition of an aqueous KOH solution (1 M; 30 ml) and subsequently cooled. The mixture was extracted with diethyl ether (3 × 30 ml), the combined extracts dried (MgSO₄). The solvent was removed in vacuo and the residue purified.

Physical data of the products, substrates, reagents, reaction time, yields, and methods of purification are given in Table 5.3. Further purification for the analytically pure sample is described for the particular compound.

Bis(2-methoxynaphthalen-1-yl)methane (5.9). A mixture of 5.7f (0.58 g, 2 mmol), 2-methoxynaphthalene (0.63 g, 4 mmol), and *p*-toluenesulfonic acid (0.38 g, 2 mmol) in toluene (30 ml) was heated under reflux for 46 h. The toluene was then removed under reduced pressure, to the residue was added NaOH solution (10%; 30 ml), extracted with methylene chloride (3 × 30 ml). The combined extract was dried (MgSO₄), the solvent removed in vacuo, and the residue purified (see Table 5.3) to give 5.9 (0.48 g, 73%). It is identical in all aspects with the sample prepared earlier.

2-(4-Dimethylaminophenylmethyl)-1,3,5-trimethoxybenzene (5.26). Obtained as plates (recrystallized from hexane). ¹H NMR δ 2.85 (s, 6 H), 3.76 (s, 6 H), 3.77 (s, 3 H), 3.83 (s, 2 H), 6.12 (s, 2 H), 6.62 (d, J = 8.7 Hz, 2 H), 7.11 (d, J = 8.7 Hz, 2 H); ¹³C NMR δ 27.1, 41.0, 55.2, 55.6, 90.6, 111.0, 112.9, 128.8, 130.7, 148.7, 158.7, 159.3.

2,2'-Methylenebis(1,3,5-trimethoxybenzene) (5.27). Obtained as microcrystals. ¹H NMR δ 3.68 (s, 12 H), 3.75 (s, 6 H), 3.84 (s, 2 H), 6.08 (s, 4 H); ¹³C NMR δ 16.5, 55.0, 55.9, 91.0, 111.8, 158.6, 159.1.

2-(2,4-Dimethoxyphenylmethyl)-1,3,5-trimethoxybenzene (5.28). Obtained as plates (recrystallized from

hexane/benzene). ^1H NMR δ 3.70 (s, 6 H), 3.71 (s, 3 H), 3.80 (s, 3 H), 3.82–3.83 (m, 5 H), 6.17 (s, 2 H), 6.27 (dd, $J = 8.3, 2.5$ Hz, 1 H), 6.43 (d, $J = 2.5$ Hz, 1 H), 6.55 (d, $J = 8.3$ Hz, 1 H); ^{13}C NMR δ 21.4, 55.10, 55.13, 55.20, 55.6, 90.5, 98.0, 103.4, 108.7, 122.0, 127.8, 158.0, 158.5, 159.2, 159.6.

Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_5$: C, 67.91; H, 6.97. Found: C, 67.96; H, 7.07.

2,4-Bis(2,4,6-trimethoxyphenylmethyl)-1,5-dimethoxybenzene (5.29). Obtained as microcrystals. ^1H NMR δ 3.50 (s, 12 H), 3.70 (s, 4 H), 3.80 (s, 6 H), 3.83 (s, 6 H), 5.94 (s, 1 H), 6.02 (s, 4 H), 6.42 (s, 1 H); ^{13}C NMR δ 21.0, 55.1, 55.3, 55.7, 90.2, 95.1, 109.3, 120.4, 127.8, 155.5, 158.9, 159.2.

Anal. Calcd for $\text{C}_{28}\text{H}_{34}\text{O}_8$: C, 67.45; H, 6.87. Found: C, 67.15; H, 6.96.

1-(4-dimethylaminophenylmethyl)-2-methoxynaphthalene (5.30). To a solution of 5.7f (0.48 g, 2 mmol) and *N,N*-dimethylaniline (0.48 g, 4 mmol) in dry toluene (20 ml) under nitrogen was added anhydrous zinc bromide (0.90 g, 4 mmol). The whole was heated under reflux for 12 h, then poured into ice-water (30 ml). The solution was extracted with diethyl ether (3 $\times$ 30 ml), the combined extract washed with water (30 ml), and dried (MgSO_4). The

solvent was removed in vacuo and the residue chromatographed (see Table 5.3) followed by recrystallization from hexane/benzene to give 5.30 (0.48 g, 83%) as plates. ^1H NMR δ 2.73 (s, 6 H), 3.79 (s, 3 H), 4.38 (s, 2 H), 6.55 (d, J = 8.5 Hz, 2 H), 7.02 (d, J = 8.2 Hz, 2 H), 7.19 (d, J = 8.9 Hz, 1 H), 7.24 (d, J = 7.7 Hz, 1 H), 7.34 (t, J = 8.0 Hz, 1 H), 7.68 (t, J = 9.5 Hz, 2 H), 7.92 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ 29.4, 40.6, 56.4, 112.8, 113.4, 122.3, 123.0, 123.8, 126.2, 127.9, 128.2, 128.7, 129.21, 129.24, 133.3, 148.7, 154.6.

Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{NO}$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.38; H, 7.34; N, 4.66.

2-Methoxy-1-[1-(4-dimethylaminophenyl)ethyl]-naphthalene (5.31). Obtained as an oil. ^1H NMR δ 1.78 (d, J = 7.3 Hz, 3 H), 2.82 (s, 6 H), 3.76 (s, 3 H), 5.20 (q, J = 7.3 Hz, 1 H), 6.62 (d, J = 8.8 Hz, 2 H), 7.1–7.3 (m, 5 H), 7.66–7.74 (m, 2 H), 7.86–7.92 (m, 1 H); ^{13}C NMR δ 18.4, 33.5, 40.8, 56.9, 112.7, 114.7, 123.0, 124.7, 125.6, 127.5, 128.1, 128.4, 128.5, 129.9, 132.5, 134.2, 148.4, 154.8. MS (HR) for $\text{C}_{21}\text{H}_{23}\text{NO}$ Calcd: 305.1764. Found: 305.1768.

2-Methoxy-1-[1-(indol-3-yl)ethyl]naphthalene (5.32). Obtained as microcrystals. ^1H NMR δ 1.89 (d, J = 7.2 Hz, 3 H), 3.79 (s, 3 H), 5.46 (q, J = 7.2 Hz, 1 H), 6.78–6.86

(m, 1 H), 6.9–7.3 (m, 7 H), 7.6–7.8 (m, 3 H), 8.18–8.22 (m, 1 H); ^{13}C NMR δ 19.3, 28.0, 56.9, 110.8, 114.5, 118.8, 119.6, 121.0, 121.2, 121.5, 123.0, 124.4, 125.5, 127.19, 127.22, 128.2, 128.6, 129.9, 132.9, 136.4, 154.5.

Anal. Calcd for $\text{C}_{21}\text{H}_{19}\text{NO}$: C, 83.69; H, 6.35; N, 4.65.
Found: C, 83.54; H, 6.48; N, 4.55.

CHAPTER VI
RING FRAGMENTATION OF
BENZOTRIAZOL-1-YL CARBANIONS

6.1 Introduction

6.1.1 Thermal and Photochemical Stability of 1-Substituted Benzotriazoles

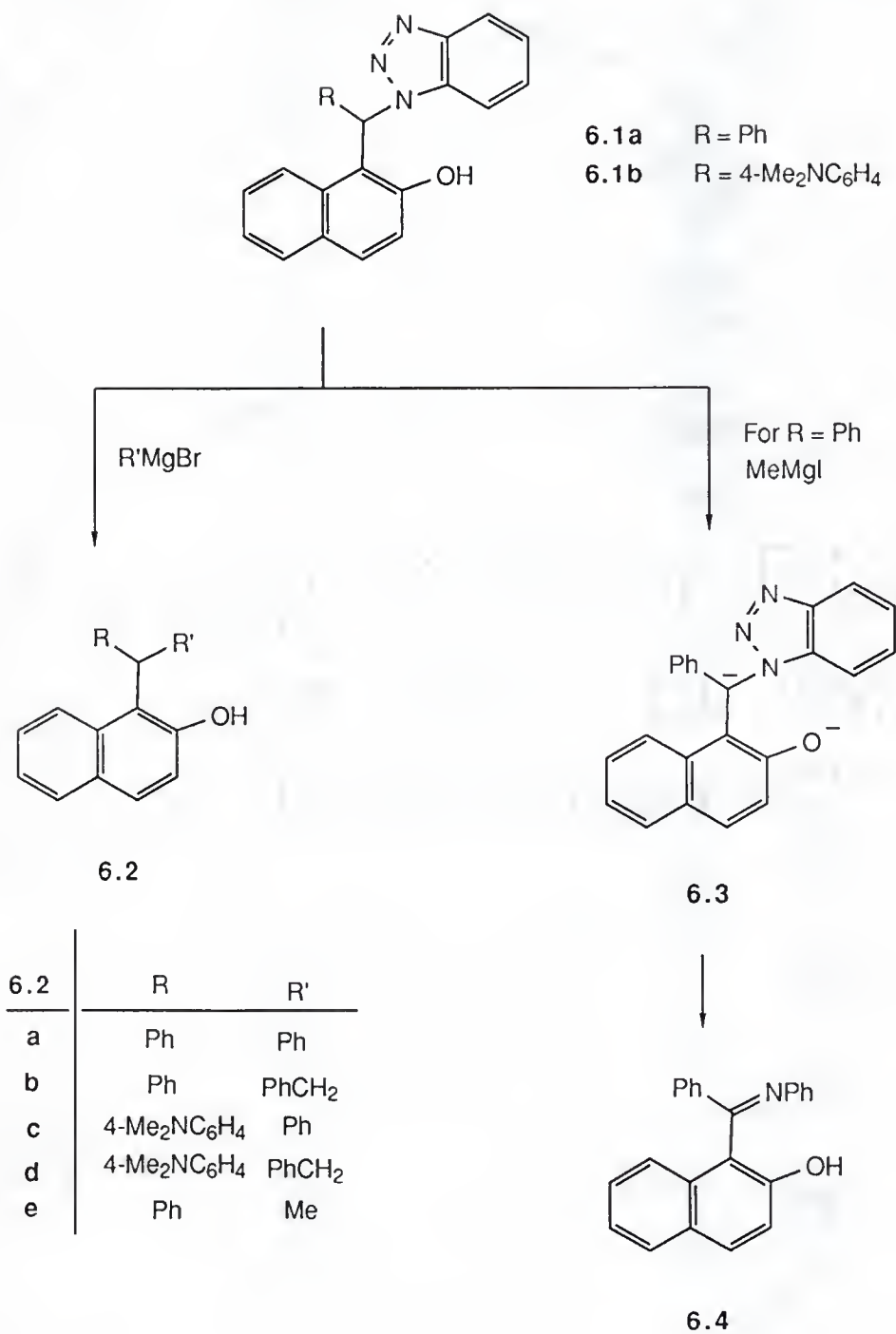
The benzotriazole ring is highly stable to acids and bases, to oxidation and reduction, and to heat. Ring opening by pyrolysis requires forcing conditions (400 °C) and 1-alkylbenzotriazoles afford complex rearranged products in low yields after elimination of nitrogen [57JCS4559]. Flash-vacuum pyrolyses (500-700 °C) of N-vinylbenzotriazoles yield N-phenylketenimines with loss of nitrogen [88JCS(P2)1071]. Photolyses of 1-substituted benzotriazoles extrude nitrogen to form biradicals [69JCS(C)1334, 70CC1089, 72BCJ515, 90JIC150], which then cyclize: thus 1-phenylbenzotriazole on irradiation gave carbazole in nearly quantitative yield [68JA1923].

In the course of the work by our group utilizing benzotriazole as a synthetic auxiliary, cleavage of the benzotriazole ring has only rarely been observed. Minor amounts of o-phenylenediamines were observed [89JOC6022, 90JCS(P1)1717] following the reaction of Grignard reagents

with 1-(α -alkoxyalkyl)- and 1-(α -aryloxyalkyl)-benzotriazoles. Reactions of 1-imidoylbenzotriazole with Grignard reagents [90CB1545] afforded a variety of products in which the triazole ring opened or was modified. In both cases, nucleophilic attack of the Grignard reagents at the benzotriazolyl nitrogen atoms was involved. A recent report [91JOC1299] demonstrated the opening of a benzotriazole ring when 1,2-di(benzotriazol-1-yl)-1,2-dichloroethane was treated with sodium azide.

6.1.2 Aim of the Work

In Chapter IV, we showed that reactions of the benzotriazole adducts 6.1 with phenyl- or benzyl-magnesium bromide gave high yields of products 6.2a-d. When a similar reaction of 6.1a was attempted with methylmagnesium iodide, instead of compound 6.2e, compound 6.4 was obtained. This could be attributed to the higher basicity and the smaller size of the methyl anion from methylmagnesium iodide as compared to the less basic and larger phenyl or benzyl anions from phenyl- or benzylmagnesium bromides (pK_a of benzene is 43 [72JA7936], pK_a of the methyl proton in toluene is 41.2 [78JA4532], while pK_a of methane is estimated to be 58 [80JA5741]). Thus, while the more basic methyl anion deprotonated both the hydroxy and the N-C α protons to form a C,O-dianion 6.3,



Scheme 6.1

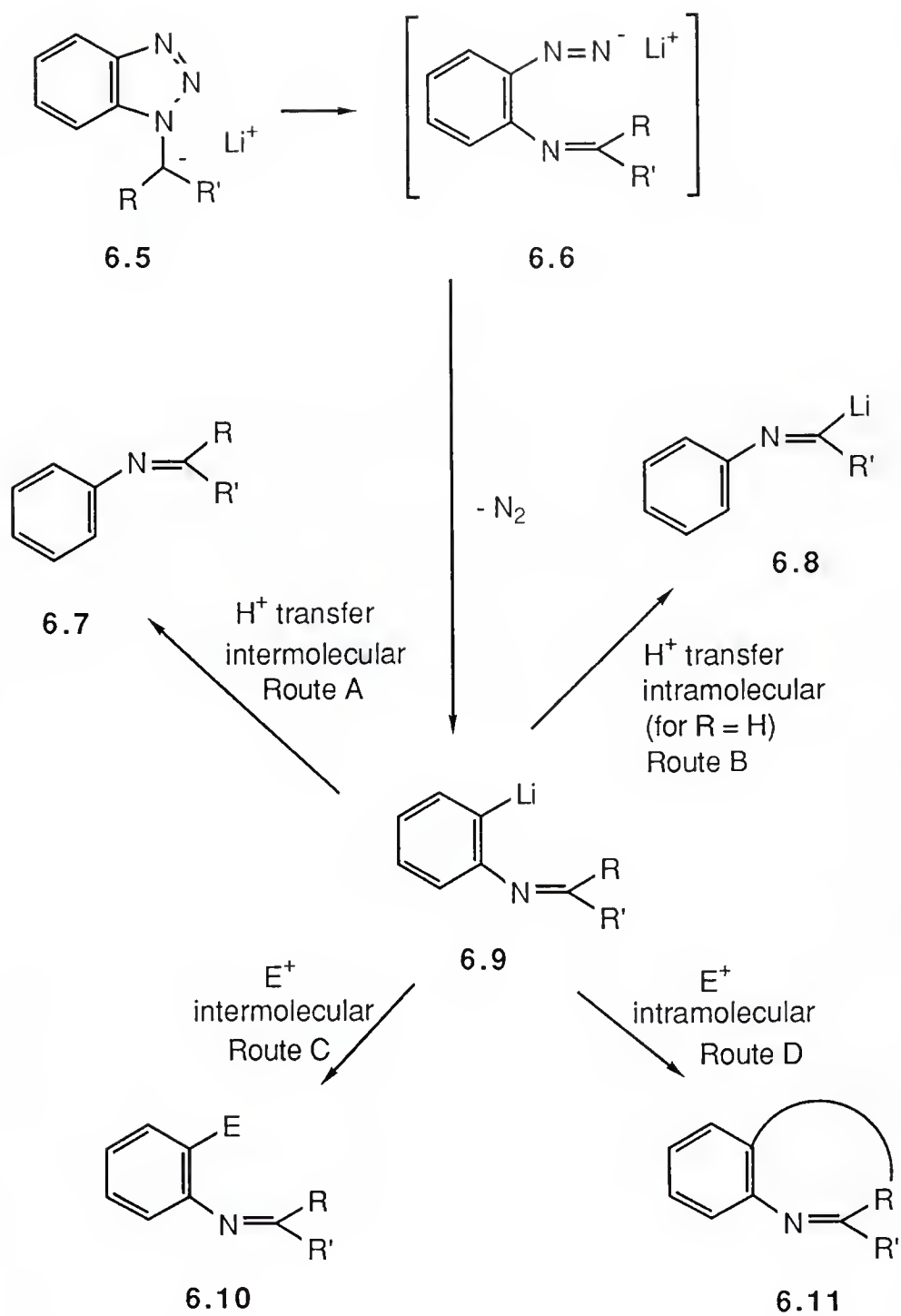
the less basic reagents only deprotonated the hydroxy proton to give the oxyanion, which then eliminated the benzotriazolyl moiety; a subsequent attack by the phenyl or benzyl anions gave the displacement products (see Chapter IV).

The objective of the project was to investigate the properties of carbanions alpha to a benzotriazol-1-yl group. Such carbanions were generated from the reaction of 1-substituted benzotriazoles with organolithium reagents.

6.2 Results and Discussion

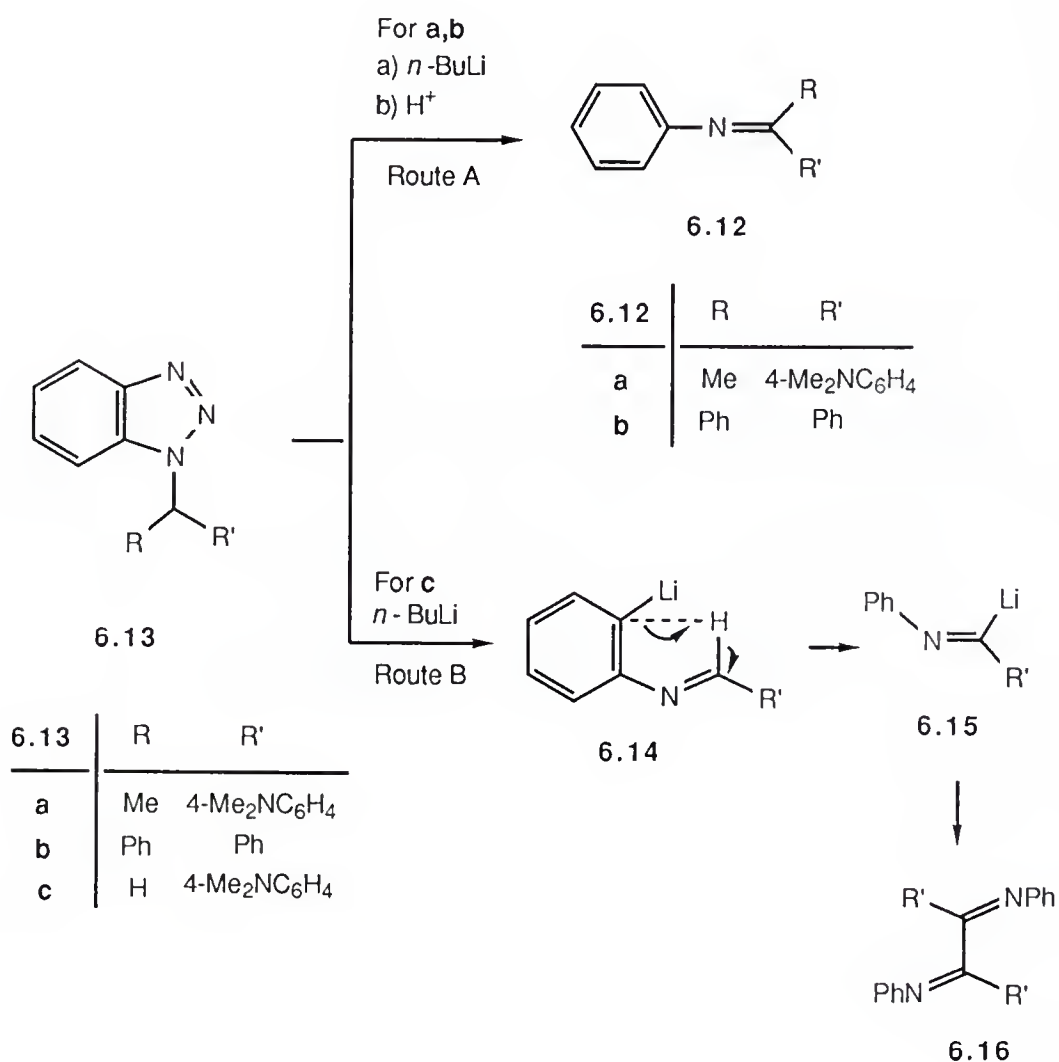
We found that the opening of the benzotriazole ring in α -benzotriazol-1-yl carbanions was a general process. The carbanions 6.5 opened via 6.6 to lose nitrogen giving intermediates 6.9 which could be protonated by inter- (to give 6.7) or intra-molecular proton transfer (to give 6.8) or be trapped by electrophiles inter- (to form 6.10) or intra-molecularly (to give heterocycles 6.11) (Scheme 6.2).

Examples of Routes A and B are given in Scheme 6.3. 4-[1-(Benzotriazol-1-yl)ethyl]-N,N-dimethylaniline (6.13a) and 1-(diphenylmethyl)benzotriazole (6.13b) on treatment with n-butyllithium (n-BuLi) gave the corresponding imines 6.12a-b via route A. On the other hand, 4-(benzotriazol-1-ylmethyl)-N,N-dimethylaniline (6.13c) gave the coupled



Scheme 6.2

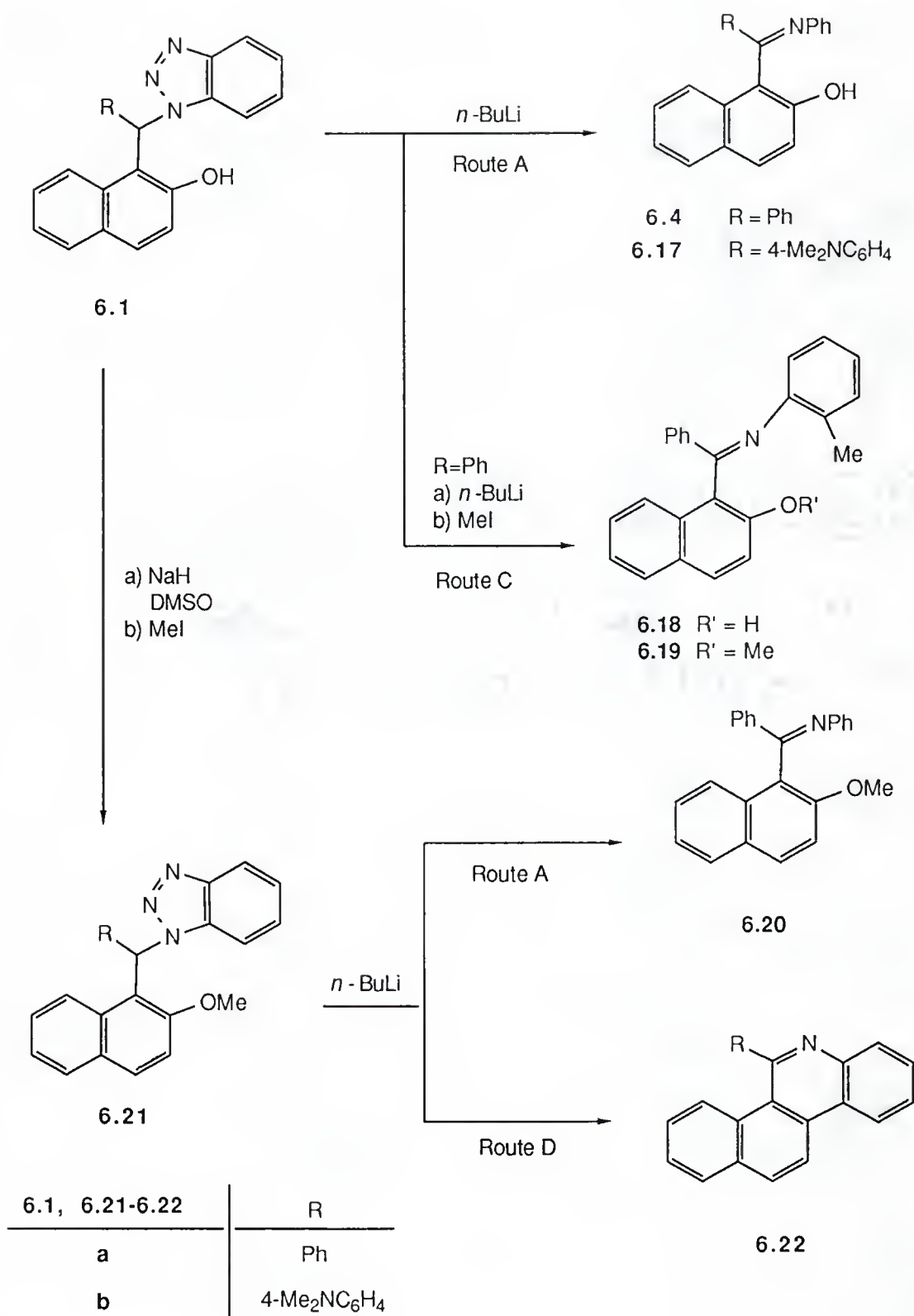
product 6.16 in a yield of 27%. Evidently, the aryllithium 6.14 deprotonated the acidic olefinic hydrogen intramolecularly (via route B) to afford the new alkenyllithium 6.15, which then coupled to give 6.16. The structure of 6.16 was confirmed by its elemental analysis and its ^{13}C NMR spectrum. The imino carbon resonated at 164.0 ppm and had no attached hydrogen according to the APT spectrum.



Scheme 6.3

Further examples of Route A and examples of Routes C and D are given in Scheme 6.4. Treatment of 6.1a,b with two equivalents of *n*-BuLi at -78 °C gave, after normal workup, imines 6.4 and 6.17 respectively via Route A. Quenching the reaction of 6.1a with two equivalents of methyl iodide prior to work-up gave a mixture of 6.18 and 6.19 (intermolecular nucleophilic attack via Route C), of which 6.18 was the major product. This can be explained by the stability of the lithio phenolate in the low dielectric medium of tetrahydrofuran. Compound 6.18 exists as a mixture of two isomers in chloroform as indicated by the presence of two sets of signals in the NMR spectra. This phenomenon could be attributed to the hydrogen bonding between the imino nitrogen and the hydroxy group making the conversion from syn- to anti- conformer and vice versa very slow. When the spectrum was recorded in the more polar dimethyl sulfoxide, the two sets of signals coalesced. When the intramolecular hydrogen bonding was not possible as in compound 6.19, only one set of signals was observed in chloroform.

Conversion of the hydroxy group in 6.1 to a methoxy group (to give 6.21) should favor intramolecular nucleophilic attack at this position (via Route D). Treatment of 6.21a with *n*-BuLi at -78 °C and then at room temperature for 12 h indeed gave the cyclized product 6.22a in a yield of 33%, accompanied by the imine 6.20 in



Scheme 6.4

Table 6.1 Preparation of Imines and Heterocycles 6.22a-b

Compound	Yield ^a (%)	M.p. (°C)	Purifi- cation ^b	$\delta_{\text{C}}(\text{C}=\text{N})$ (ppm)
6.4	69	176-178 ^c	10:1 ^d	164.6
6.12a	74	109-111	12:1 ^d	164.3
6.12b	51	110-112 ^e	15:1 ^d	168.2
6.16	27	246-248	15:1 ^d	164.0
6.17	78	211-213	8:1 ^d	164.3
6.18	89	165-167	2:1 ^d	163.6
6.19	4	102-104	2:1 ^d	163.3
6.20	45	108-110	1:1 ^f	165.1
6.22a	82	156-158	2:1 ^f	159.2
6.22b	78	220-222	12:1 ^d	159.3

^a Isolated yields.

^b Purification of the crude product by column chromatography. Further purification for the analytically pure sample is described in the Experimental section.

^c Lit. [66BSF1721] m.p. 178 °C.

^d Petroleum ether (38-56 °C)/EtOAc, v/v.

^e Lit. [34JA2095] m.p. 112-113 °C.

^f Petroleum ether (38-56 °C)/CH₂Cl₂, v/v.

45% yield. The ¹H and ¹³C NMR spectra of 6.22a displayed no signals in the aliphatic region showing that the methoxy group was not present. The structure of 6.22a was further confirmed by the mass spectrum and by the

elemental analysis. Increasing the reaction time to 2 days gave the cyclized product 6.22a exclusively (82%). Similarly 6.22b was obtained in a yield of 78%.

All the imines prepared display characteristic C=N signals in the ^{13}C NMR spectra between 163.3–168.2 ppm. The C=N signals for the heterocycles 6.22a,b are at 159.2 and 159.3 ppm, respectively (Table 6.1).

6.3 Conclusions

Although the benzotriazole ring has proved to be extremely stable during its wide applications as a synthetic auxiliary in organic transformations, we have demonstrated here that the presence of an anion adjacent to the benzotriazol-1-yl group makes the triazole susceptible to ring opening. This is the first example of the benzotriazole ring opening to form imines under mild conditions.

6.4 Experimental

The apparatus and general procedures applied in this Chapter are identical to those described in Chapters II and III with the following additions.

Column chromatography was carried out on MBS silica gel (230–400 mesh).

1-(Diphenylmethyl)benzotriazole (6.13b) was prepared

according to the literature procedure, m.p. 153–155 °C (Lit. [85H2895] m.p. 153–155 °C). 4-[1-(Benzotriazol-1-yl)ethyl]-N,N-dimethylaniline (6.13a), 4-(benzotriazol-1-ylmethyl)-N,N-dimethylaniline (6.13c), and compounds 6.1a–b were prepared according to the methods described in the previous chapters (for 6.13a, see Chapter III; for 6.13c, see Chapter II; for 6.1a–b, see Chapter IV).

6.4.1 General Procedure for the Preparation of Compounds 6.4, 6.12, 6.16, 6.17, 6.20, and 6.22

To a solution of the substrate (1.0 mmol) in THF (20 ml) at –78 °C was added the appropriate amount of n-BuLi (2.5 M in hexane; for the preparation of 6.12, 6.16, 6.20, and 6.22, 1.1 mmol of n-BuLi was added; for the preparation of 6.4 and 6.17, 2.2 mmol of n-BuLi was added.). The resulting solution was allowed to warm slowly to room temperature overnight, poured into water (20 ml), extracted with diethyl ether (3 × 30 ml). The combined extracts were dried (MgSO₄), the solvent removed in vacuo, and the residue purified.

Physical data of the products, yields, and methods of purification are given in Table 6.1. Further purification for the analytically pure sample is described for each individual compound.

1-(N-Phenylbenzimidoyl)-2-naphthol (6.4). Obtained as microcrystals (recrystallized from hexane/EtOAc). ¹H NMR δ

6.7-7.0 (m, 5 H), 7.1-7.5 (m, 7 H), 7.6-7.8 (m, 4 H), 9.46 (s, 1 H); ^{13}C NMR δ 115.8, 117.0, 118.5, 122.0, 122.4, 123.3, 125.8, 126.8, 127.1, 127.2, 127.4, 129.1, 129.7, 130.9, 138.2, 150.6, 151.6, 164.6.

4-[(1-Phenylimino)ethyl]-N,N-dimethylaminoaniline (6.12a). Obtained as plates (recrystallized from hexane/benzene). ^1H NMR δ 2.15 (s, 3 H), 2.99 (s, 6 H), 6.69 (d, $J = 8.8$ Hz, 2 H), 6.76-6.80 (m, 2 H), 6.99-7.05 (m, 1 H), 7.27-7.33 (m, 2 H), 7.88 (d, $J = 8.8$ Hz, 2 H); ^{13}C NMR δ 16.8, 40.1, 111.2, 119.8, 122.5, 127.1, 128.4, 128.7, 151.8, 152.3, 164.3.

Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.28; H, 7.81; N, 11.46.

N-(Diphenylmethylenidene)aniline (6.12b). Obtained as microcrystals (recrystallized from hexane/benzene). ^1H NMR δ 6.71 (d, $J = 7.4$ Hz, 2 H), 6.90 (t, $J = 7.4$ Hz, 1 H), 7.1-7.5 (m, 10 H), 7.7-7.8 (m, 2 H); ^{13}C NMR δ 120.9, 123.1, 127.8, 128.1, 128.4, 128.5, 129.3, 129.5, 130.7, 136.2, 139.6, 151.2, 168.2.

1,2-Bis(4-dimethylaminophenyl)-1,2-bis(phenylimino)ethane (6.16). Obtained as microcrystals (recrystallized from hexane/EtOAc). ^1H NMR δ 3.01 (s, 12 H), 6.47 (d, $J = 7.6$ Hz, 4 H), 6.65 (d, $J = 9.2$ Hz, 4 H), 6.9-7.1 (m, 6 H),

7.79 (d, $J = 9.2$ Hz, 4 H); ^{13}C NMR δ 40.1, 111.8, 120.5, 123.8, 126.2, 128.1, 130.0, 150.2, 151.8, 164.0.

Anal. Calcd for $\text{C}_{30}\text{H}_{30}\text{N}_4$: C, 80.65; H, 6.81; N, 12.36. Found: C, 80.68; H, 6.77; N, 12.55.

1-(N-Phenyl-4-dimethylaminobenzimidoyl)-2-naphthol (6.17). Obtained as microcrystals (recrystallized from hexane/EtOAc). ^1H NMR δ 2.95 (s, 6 H), 6.58 (d, $J = 9.2$ Hz, 2 H), 6.68–6.74 (m, 1 H), 6.83–6.95 (m, 4 H), 7.09 (d, $J = 8.9$ Hz, 2 H), 7.14–7.28 (m, 2 H), 7.50 (d, $J = 8.4$ Hz, 1 H), 7.56–7.65 (m, 3 H), 9.0 (br, 1 H); ^{13}C NMR δ 39.7, 110.8, 116.9, 117.3, 119.3, 122.2, 122.3, 124.2, 125.9, 126.4, 127.2, 127.3, 129.1, 129.5, 131.7, 151.5, 151.6, 164.3.

Anal. Calcd for $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}$: C, 81.94; H, 6.05; N, 7.64. Found: C, 81.94; H, 6.15; N, 7.58.

1-(N-Phenylbenzimidoyl)-2-methoxynaphthalene (6.20). Obtained from the reaction of 6.21a with *n*-BuLi (at room temperature for 12 h) as plates (recrystallized from hexane/benzene). ^1H NMR δ 3.66 (s, 3 H), 6.7–6.8 (m, 2 H), 6.93 (t, $J = 7.5$ Hz, 2 H), 7.07 (d, $J = 9.1$ Hz, 1 H), 7.2–7.4 (m, 6 H), 7.52 (d, $J = 8.8$ Hz, 1 H), 7.63 (d, $J = 7.9$ Hz, 1 H), 7.70 (d, $J = 9.0$ Hz, 1 H), 7.74–7.79 (m, 2 H); ^{13}C NMR δ 55.9, 112.3, 119.1, 119.6, 123.2, 123.6, 124.7, 126.9, 127.8, 128.0, 128.2, 128.3, 130.4, 130.6, 131.8, 139.0, 151.4, 153.6, 165.1.

Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15.
Found: C, 85.10; H, 5.68; N, 4.04.

1-Phenylbenzo[i]phenanthridine (6.22a). Obtained from the reaction of 6.21a with *n*-BuLi [(33%) at room temperature for 12 h; (82%) at room temperature for 48 h] as needles (recrystallized from hexane/benzene). ^1H NMR δ 7.15–7.25(m, 1 H), 7.4–7.8 (m, 9 H), 7.88 (d, J = 7.2 Hz, 1 H), 8.09 (d, J = 8.8 Hz, 1 H), 8.26 (dd, J = 8.2, 1.3 Hz, 1 H), 8.58 (d, J = 9.2 Hz, 2 H); ^{13}C NMR δ 119.8, 121.4, 122.4, 123.5, 125.8, 126.3, 126.7, 128.2, 128.3, 128.4, 128.8, 128.9, 129.0, 129.9, 130.2, 132.2, 133.1, 134.3, 144.0, 144.5, 159.2.

Anal. Calcd for $C_{23}H_{15}N$: C, 90.46; H, 4.95; N, 4.59.
Found: C, 90.34; H, 4.96; N, 4.47.

1-(4-Dimethylaminophenyl)benzo[i]phenanthridine (6.22b). Obtained from reaction of 6.21b with *n*-BuLi (at room temperature for 48 h) as plates (recrystallized from hexane/benzene). ^1H NMR δ 2.96 (s, 6 H), 6.76 (d, J = 8.9 Hz, 2 H), 7.18–7.22 (m, 1 H), 7.4–7.6 (m, 4 H), 7.66–7.73 (m, 1 H), 7.81 (dd, J = 7.9, 1.3 Hz, 1 H), 8.00 (d, J = 8.8 Hz, 1 H), 8.05 (d, J = 8.6 Hz, 1 H), 8.19–8.24 (m, 1 H), 8.45–8.51 (m, 2 H); ^{13}C NMR δ 40.4, 112.5, 119.6, 121.4, 122.2, 123.1, 125.4, 126.0, 126.1, 128.1, 128.3, 128.7, 129.6, 129.9, 130.6, 131.8, 132.4, 133.0, 134.1, 144.1, 150.6, 159.3.

Anal. Calcd for $C_{25}H_{20}N_2$: C, 86.18; H, 5.79; N, 8.04.
Found: C, 85.99; H, 5.76; N, 7.84.

Procedure for the Preparation of Compounds 6.18 and 6.19. To a solution of 6.1a (0.70 g, 2 mmol) in THF (40 ml) at $-78\text{ }^{\circ}\text{C}$ was added *n*-BuLi (2.5 M in hexane; 1.6 ml, 4.0 mmol). The resulted solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and at room temperature for 2 h. It was again cooled to $-78\text{ }^{\circ}\text{C}$ and methyl iodide (0.60 g, 4.2 mmol) was added. After allowing the solution to reach room temperature overnight, ammonium chloride solution (20%; 30 ml) was added. The organic phase was separated, the aqueous phase was extracted with diethyl ether (3 $\times$ 30 ml). The combined organic phases were washed with water (30 ml) and dried (MgSO_4). The solvent was removed in vacuo, the residue chromatographed (see Table 6.1) to give compounds 6.18 (0.6 g, 89%) as microcrystals and 6.19 (0.04 g, 4%) as microcrystals.

1-[N-(2-Methylphenyl)benzimidoyl]-2-naphthol (6.18).

^1H NMR ($\text{DMSO}-d_6$) δ 2.33 (s, 3 H), 6.6–6.8 (m, 3 H), 6.9–7.1 (m 1 H), 7.1–7.5 (m, 7 H), 7.7–7.8 (m, 4 H), 10.1 (broad, 1 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 17.8, 116.0, 116.9, 117.7, 122.8, 123.3, 123.6, 125.4, 126.6, 127.3, 127.9, 128.2, 128.5, 129.1, 129.6, 130.0, 130.6, 131.7, 138.8, 149.2, 152.7, 163.6.

Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15.
Found: C, 85.20; H, 5.84; N, 3.81.

1-[N-(2-Methylphenyl)benzimidoyl]-2-methoxy-
naphthalene (6.19). ^1H NMR δ 2.36 (s, 3 H), 3.70 (s, 3 H),
6.4–6.5 (m, 1 H), 6.58–6.76 (m, 2 H), 6.9–7.4 (m, 7 H),
7.52–7.56 (m, 1 H), 7.7–7.8 (m, 4 H); ^{13}C NMR δ 17.9,
55.8, 112.4, 117.2, 119.5, 123.4, 123.5, 123.6, 124.8,
125.2, 126.8, 128.1, 128.2, 128.3, 129.5, 129.8, 130.3,
130.4, 132.5, 139.3, 149.5, 153.7, 163.3.

Anal. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99.
Found: C, 85.63; H, 6.17; N, 3.82.

6.4.2 General Procedure for the Preparation of Compounds 6.21

Sodium hydride (60% in mineral oil; 0.24 g, 6 mmol) was added to an ice-cold solution of the corresponding 6.1 (5 mmol) in dimethyl sulfoxide (10 ml). The solution was stirred at room temperature for 15 min and methyl iodide (1.4 g, 10 mmol) was added. The resulted solution was stirred at room temperature for 10 min, poured into ice-water (30 ml) and extracted with diethyl ether (3 $\times$ 30 ml). The combined extracts were washed with water (4 $\times$ 30 ml) and dried ($MgSO_4$). The solvent was removed in vacuo to give the essentially pure product 6.21. Purification for the analytically pure sample is described for the individual compound.

1-[α -(Benzotriazol-1-yl)benzyl]-2-methoxynaphthalene (6.21a). Obtained in 91% as plates (recrystallized from hexane/benzene), m.p. 167-169 °C. ^1H NMR δ 3.70 (s, 3 H), 7.1-7.3 (m, 11 H), 7.72 (d, J = 7.8 Hz, 1 H), 7.83 (d, J = 9.0 Hz, 1 H), 8.00-8.05 (m, 1 H), 8.16 (d, J = 8.5 Hz, 1 H), 8.35 (s, 1 H); ^{13}C NMR δ 56.4, 58.8, 110.7, 113.1, 118.0, 119.7, 123.5, 123.7, 124.7, 126.8, 126.9, 127.4, 127.8, 128.4, 129.6, 131.5, 132.4, 134.0, 137.5, 145.6, 155.5.

Anal. Calcd for $\text{C}_{24}\text{H}_{19}\text{N}_3\text{O}$: C, 78.88; H, 5.24; N, 11.50. Found: C, 78.77; H, 5.27; N, 11.37.

1-[1-(Benzotriazol-1-yl)-1-(4-dimethylaminophenyl)]-methyl-2-methoxynaphthalene (6.21b). Obtained in 85% as microcrystals (recrystallized from hexane/benzene), m.p. 156-158 °C. ^1H NMR δ 2.92 (s, 6 H), 3.62 (s, 3 H), 6.65 (d, J = 9.0 Hz, 2 H), 7.05-7.12 (m, 3 H), 7.2-7.4 (m, 5 H), 7.75 (dd, J = 7.8, 1.1 Hz, 1 H), 7.84 (d, J = 9.0 Hz, 1 H), 7.98-8.03 (m, 1 H), 8.13 (d, J = 8.5 Hz, 1 H), 8.23 (s, 1 H); ^{13}C NMR δ 40.3, 56.4, 59.6, 111.3, 112.2, 113.4, 118.9, 119.6, 123.2, 123.5, 123.6, 124.3, 126.5, 126.9, 128.5, 129.5, 129.6, 130.9, 132.4, 134.1, 145.7, 150.1, 155.3.

Anal. Calcd for $\text{C}_{26}\text{H}_{24}\text{N}_4\text{O}$: C, 76.45; H, 5.92; N, 13.72. Found: C, 76.40; H, 5.99; N, 13.72.

CHAPTER VII SUMMARY

The use of benzotriazole as a synthetic auxiliary has been extended to conjugated systems, where a benzene ring has acted as the relay group and an amino, a hydroxy, or a methoxy group has provided the hetero atom bearing an electron pair to assist in the displacement of the benzotriazole group.

In Chapters II and III, N-(benzotriazol-1-ylmethyl)-anilines were shown to react with arylamine hydrochlorides to give bis(4-aminoaryl)methanes. The reactions of an aniline with 1-hydroxymethylbenzotriazole afforded the symmetrical methylenebisaniline when two equivalents of the aniline was used. With one equivalent of the aniline, a mixture of the 4-(benzotriazol-1-yl)aniline and the corresponding methylenebisaniline was obtained. The benzotriazole group in 4-(benzotriazol-1-ylmethyl)anilines was displaced by various electron-rich aromatic nucleophiles, i.e. anilines, 1,3-dimethoxybenzene, 1,3,5-trimethoxybenzene, pyrroles, and indoles, forming the respective diarylmethanes in good yields.

The methylene groups in 4-(benzotriazol-1-ylmethyl)-anilines were proved to be quite acidic and were deprotonated with organolithium reagents. The anions were

trapped by a variety of electrophiles. A subsequent displacement of the benzotriazole group in the lithiated derivatives gave leuco dyestuffs.

In Chapter IV, phenols and naphthols were shown to react with 1-hydroxymethylbenzotriazole to give ortho substituted derivatives. When both the ortho positions were blocked, the alkylation occurred at the para position. While phenol failed to condense with aldehydes and benzotriazole, naphthols did so to give mixtures of benzotriazol-1-yl and 2-yl isomers. The protection of the phenolic hydroxyl group with trimethylsilyl chloride enabled an efficient substitution at the methylene group via lithiation. This was the first example of such a directed lithiation in phenols using a protection strategy. The benzotriazole group in the parent and the lithiated derivatives was displaced by Grignard reagents and by hydride ion from lithium aluminum hydride.

In Chapter V, an investigation was carried out for phenol ethers similar to that for phenols. The reactions of phenol ethers with 1-hydroxymethylbenzotriazole gave, contrary to those for phenols, para substituted derivatives. If the para position was blocked, the substitution occurred at the ortho position. The methylene groups were easily substituted with electrophiles via lithiation. The benzotriazolyl moiety in these derivatives, depending on the substrates, was displaced by

Grignard reagents and by nucleophilic aromatic compounds such as anilines and indole.

In Chapter VI, the opening of the benzotriazole ring of the α -benzotriazol-1-yl carbanions was investigated. Such carbanions were generated by the reaction of organolithium reagents with 1-substituted benzotriazoles. The smooth opening of the triazole ring was observed followed by the loss of a molecule of nitrogen to give an anion, which was trapped by electrophiles inter- or intramolecularly to give imines or heterocycles.

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Letter Codes for Journal Titles

<u>Code</u>	<u>Journal Abbreviation</u>
ACR	Acc. Chem. Res.
AC(R)	Ann. Chim. (Rome)
ACS	Acta Chem. Scan.
AG	Angew. Chem.
BCJ	Bull. Chem. Soc. Jpn

BRP	Br. Pat.
BSF	Bull. Soc. Chim. Fr.
CB	Chem. Ber.
CC	J. Chem. Soc., Chem. Commun.
CCC	Collect. Czech. Chem. Commun.
CJC	Can. J. Chem.
CL	Chem. Lett.
CRV	Chem. Rev.
CSR	Chem. Soc. Rev.
FRP	Fr. Pat.
GEP	Ger. Pat.
H	Heterocycles
HCA	Helv. Chim. Acta
IJC(B)	Indian J. Chem., Sect. B
JA	J. Am. Chem. Soc.
JAP	Jpn. Pat.
JCR(S)	J. Chem. Res. (S)
JCS	J. Chem. Soc.
JCS(C)	J. Chem. Soc. (C)
JCS(P1)	J. Chem. Soc., Perkin Trans. 1.
JCS(P2)	J. Chem. Soc., Perkin Trans. 2.
JHC	J. Heterocycl. Chem.
JIC	J. Indian Chem. Soc.
JMC	J. Med. Chem.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.

LA	Liebigs Ann. Chem.
MI	Miscellaneous
NEP	Neth. Pat.
OMR	Org. Magn. Reson.
OR	Org. React.
OSC	Org. Synth., Coll. Vol.
RTC	Recl. Trav. Chim., Pays-Bas
S	Synthesis
SC	Synth. Commun.
T	Tetrahedron
TL	Tetrahedron Lett.
USP	U.S. Pat.
UP	Unpublished Results
ZOR	Zh. Org. Khim.

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